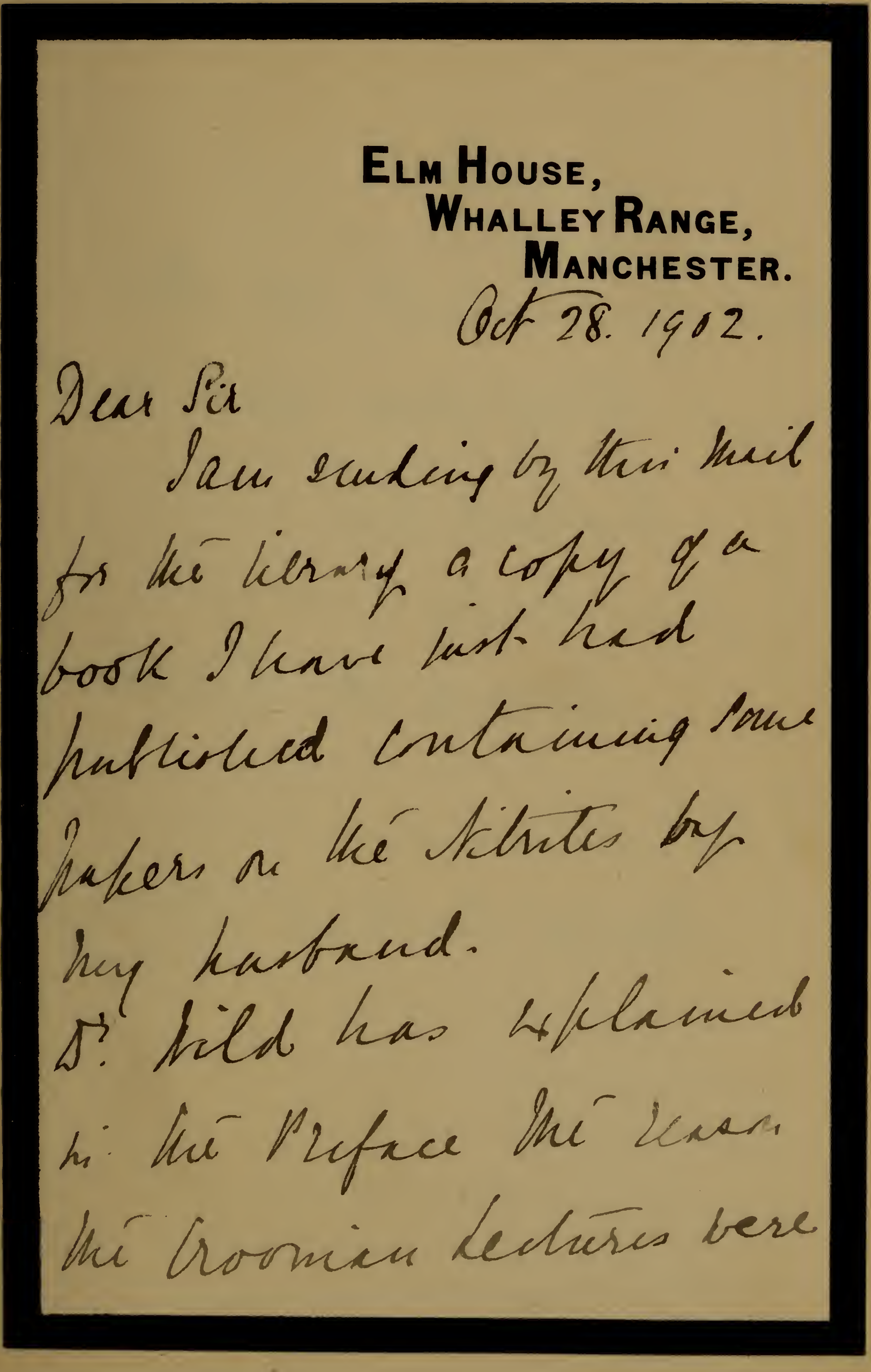
Presented to the Medical Library
of Boston. Mass.
by Mrs Leech
in memory of the late D. J. Leech. M.D. D.Sc. F.R.C.P.
Professor of Materia Medica & Therapeutics
in The Owens College



Elm House,
Whalley Range,
Manchester.

Oct 28. 1902.

Dear Sir

I am sending by this mail for the library a copy of a book I have just had published containing some papers on the Nitrites by my husband.

Dr. Wild has explained in the Preface the reason the Croonian Lectures were

not published at the
time they were delivered

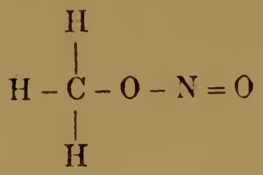
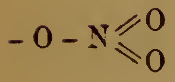
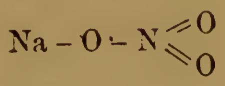
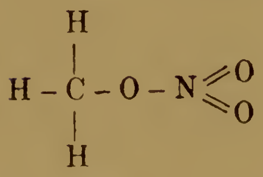
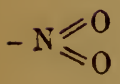
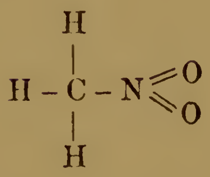
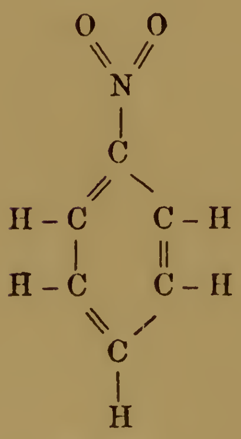
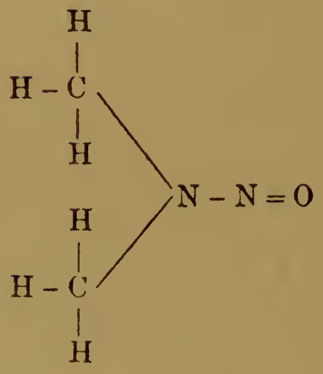
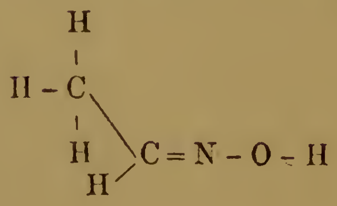
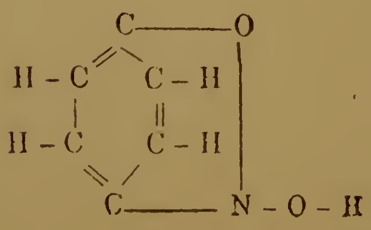
Believe me
Yours truly
Louisa M. Leech.

To the Librarian
Boston Medical Library

THE PHARMACOLOGICAL ACTION AND THERAPEUTIC USES OF THE NITRITES AND ALLIED COMPOUNDS,

INCLUDING

THE CROONIAN LECTURES FOR 1893.

GROUPS.		EXAMPLES.		
$-O-N=O$	Nitrites	$Na-O-N=O$	Sodium Nitrite	$NaNO_2$
		 $\begin{array}{ccccccccc} & & H \\ & & \vert \\ H & - & C & - & O & - & N & = & O \\ & & \vert \\ & & H \end{array}$	Methyl Nitrite	CH_3NO_2
	Nitrates		Sodium Nitrate	$NaNO_3$
			Methyl Nitrate	CH_3NO_3
	Nitro Compounds		Nitro-methane	CH_3NO_2
			Nitro-benzene	$C_6H_5NO_2$
$=N=N=O$	Nitrosamines		Dimethyl Nitrosamine	$(CH_3)_2NNO$
$-O-N=N-O-$	Hyponitrites	$Na-O-N=N-O-Na$	Sodium Hyponitrite	$Na_2N_2O_2$
$=N-O-H$	Oximes		Aldoxime	CH_3CHNOH
			Quinoxime Nitrosophenol	C_6H_4ONOH

THE PHARMACOLOGICAL ACTION AND THERAPEUTIC USES

OF THE

NITRITES AND ALLIED COMPOUNDS

INCLUDING

THE CROONIAN LECTURES FOR 1893.

BY THE LATE

DANIEL JOHN LEECH, M.D. (Lond.), D.Sc. (Vict.), F.R.C.P.,
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PROFESSOR OF MATERIA MEDICA AND THERAPEUTICS IN
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MANCHESTER: SHERRATT & HUGHES.
1902.

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PREFACE.

The late Professor Leech had always intended to republish his Croonian Lectures in book form, with considerable additions and a larger number of illustrations. The pressure of an exceedingly busy life prevented him from carrying out this intention at the time and it was postponed until—as he hoped—lessened hospital claims would afford him more leisure for literary work.

His early death in July, 1900, frustrated not only this purpose but also more important literary projects which he had in mind and for which he had collected much material.

To many of his friends it has seemed desirable to carry out his intention, as far as possible, by collecting into one volume his various papers upon the Nitrites and allied compounds together with the relative portions of the extensive Bibliography of Materia Medica which he had compiled.

No alterations have been made in the text of the earlier papers. The Croonian Lectures have, however, been revised, divided into chapters for greater convenience, and many additional figures have been added.

The lecture on the relation of Pharmacology to Therapeutics has been prefixed because it affords a valuable indication of the lines upon which Professor Leech taught and upon which he conducted his own researches, and also forms a suitable introduction to the other papers.

Though the date of the Croonian Lectures was 1893 the present volume represents the views held by Professor Leech in 1900 when he contributed the article upon the Nitrite group to the *Text-Book of Pharmacology and Therapeutics*, edited by Dr. Hale White, and published in 1901. Before writing that article he revised a copy of the Croonian Lectures and use has been made of the revised copy in preparing this volume.

Mr. Ernest Leech, B.A., M.B. (Cantab), has given much valuable help in verifying the references and correcting the proofs and has prepared the index.

ROBERT BRIGGS WILD.

MANCHESTER,
April, 1902.

THE RELATION OF PHARMACOLOGY TO THERAPEUTICS.

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THE RELATION OF PHARMACOLOGY TO THERAPEUTICS.

1884.

As an introduction to the course of lectures on pharmacology and therapeutics this session,[1] I propose to set forth the relation between these two subjects and to discuss the basis of our present system of therapeutics, which is intimately connected with this relation.

Let me point out that the word pharmacology is used here in its narrower sense. Formerly it included every department relating to medicines—pharmacognosy, pharmacy, and pharmacodynamics or the effects and uses of drugs. But it has been found convenient to restrict its meaning, and pharmacology is now understood to mean that department which relates to the action of drugs on the body and its organs.

It is the bearing then of our knowledge of the physiological action of drugs on therapeutics—that is on their application in the cure of disease—that I propose to discuss to-day, and this involves in the first place an inquiry into the grounds of our therapeutic procedures.

Now we may best approach this part of the subject by considering the lines on which we proceed in the selection of a remedy when a case of disease presents itself for medicinal treatment. It will be found, I believe, that we always do one or other or both of two things—we call to mind our own experience and the experience related by others as to the drug found useful under similar circumstances; or we choose a drug by the aid of a train of reasoning involving one or more theories or hypotheses as to the relation which exists between the known or supposed properties of the drug and the known or supposed conditions in the case before us; or, and this perhaps is our commonest proceeding, we combine the two methods and select a remedy partly from such reasoning and partly from experience. The changes which have taken place in therapeutic practice from the remotest ages to the present time have been partly due to changes in our power of estimating experience and evolving hypotheses, but they have been likewise connected with the *relative value* attached to experience and hypothesis at different periods.

---

[1] May, 1884.

In the earliest ages to which our knowledge of therapeutic procedures extends, the experience on which reliance was placed was of the simplest kind. "The Chaldeans and Babylonians, we are told by Herodotus, carried their sick to the public roads and markets that travellers might converse with them and communicate such remedies as had been successfully employed in similar cases. This custom continued for many ages in Assyria, and Strabo says it prevailed amongst the ancient Lusitanians or Portuguese."[1] Exactly the same kind of experience was utilised which is now relied on by those ignorant of medicine—Mr. A has a cough, and is recommended by his friend to take a medicine which has cured Mr. B, without any consideration being given to the cause of the cough, the identity or even close analogy of the symptoms, or the nature of the remedy. The nail is sometimes hit on the head—the remedy suggested by this crude kind of experience is successful. In the hands of those very capable of appreciating indications of real likeness between cases of disease, striking results have been frequently obtained, and hence we have had sects, as indeed we now have individuals, calling themselves empirics and boasting of their reliance on experience, to the exclusion of all theory. The origin of the term empiricism indicates the weak point of the boast. It is derived from πεῖρα, a trial, and when in therapeutics we act according to experience, we in fact only make trial of a remedy which *we think* we have seen do good in a case where *we think* the conditions have been similar to those in the case before us. Every adaptation in the use of a drug founded on experience is in fact an experiment which we make on the ground of two judgments—(1) that in the former case or cases the drug actually did good; (2) that in the present case the essential conditions of the experiment are the same as in the former. The father of medicine says in his first aphorism, ἡ δὲ πεῖρα σφαλερὴ, ἡ δὲ κρίσις χαλεπή—"Experience is delusive, judgment is difficult;" and so it has ever been found. Constantly have experiences proved delusive because of misjudgments as to the real effects of a drug, or as to the similarity of the instances of disease. An anecdote recorded by Paris[1] in his history of Sir Humphrey Davy, and also mentioned in the "Pharmacologia," illustrates well one cause of the difficulty in deciding as to the true effects of the drug. It is interesting not only in connection with my subject, but because it seems to show that this great English observer was one of the first to appreciate the value of the thermometer in exact observations on the human body.

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[1] Paris, "Pharmacologia." 9th ed., p. 9.

"As soon," says Paris, "as the powers of nitrous oxide were discovered, Dr. Beddoes at once concluded it must necessarily be a specific for paralysis; a patient was selected for trial, and the management of it was entrusted to Davy. Previous to the administration of the gas, he inserted a small pocket thermometer under the tongue of the patient, as he was accustomed to do upon such occasions to ascertain the degree of animal temperature, with a view to future comparison. The paralytic man, wholly ignorant of the nature of the process to which he was to submit, but deeply impressed from the representations of Dr. Beddoes, with the certainty of success, no sooner felt the thermometer under his tongue than he concluded the talisman was in full operation, and in a burst of enthusiasm declared he already experienced the effect of its benign influence throughout his body. The opportunity was too tempting to be lost. Davy cast an intelligent glance at Mr. Colridge," who communicated the anecdote to Paris, " and desired his patient to renew his visit on the following day, when the same ceremony was performed and repeated every succeeding day for a fortnight, the patient gradually improving during that period, when he was discharged as cured, no other application having been used."

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[1] "Life of Sir Humphrey Davy," by J. A. Paris, M.D., F.R.S., 1831, p. 50.

It was fortunate that the patient recovered under the use of the thermometer before the nitrous oxide gas could get the credit of the cure.

Here want of diagnostic power nearly led to an erroneous judgment. The cause of the man's paralysis was doubtless volitional defect, not structural lesion. The case was one of a class now well known, in which an efficient stimulus to volition is alone required for recovery, and in which a mental influence may supply the needed stimulus. Had Dr. Beddoes recognised this he would not have attempted to estimate the value of the gas in paralysis by giving it to this man. Diagnosis has improved since the time of Dr. Beddoes, yet still we at times erroneously think we cure because we fail to recognise the real nature of the disease we treat.

But a power of diagnosing correctly will not save us from misjudgments as to the real effect of drugs if we do not also know the natural history of disease, its tendencies to change in features and to recovery, apart from drug influence. The absence of this knowledge has rendered reliance on experience wofully deceptive, as the history of the treatment of pneumonia well shows. It is an oft-told tale, but its lessons cannot be too firmly impressed on those who practise medicine.

At the beginning of this century the treatment of pneumonia by bleeding and large doses of tartar emetic was everywhere general, almost universal indeed, in England. Medical men knew that a majority of cases of pneumonia coming under their care recovered when bled or dosed with antimony. They saw from time to time, too, among the poorer classes whose poverty prevented medical aid being called in early, advanced cases of pneumonia hitherto untreated apparently moribund, and in such cases treatment never seemed to avail much: almost all died. They believed, therefore, that patients recovered owing to the bleeding, and that the majority not subjected to this treatment died for want of it. And so when called in to a case of pneumonia they did not venture to try the experiment of omitting the employment of a means which they considered almost essential to the recovery of a patient seriously affected. There were some, it is true, who raised their voices against indiscriminate active treatment, who pointed out instances of recovery without it, and suggested the possibility that bleeding and recovery were sequences, not cause and effect. The voices of these men, however, were comparatively feeble, and their views gained ground but slowly. But then came Hahnemann's hypothesis, and as a consequence the administration of infinitesimal doses. Medical men, hearing of case after case of pneumonia which had recovered under infinitesimals, became emboldened to dispense with remedies hitherto thought essential, and hospital records were in time published which showed that a large percentage of cases of pneumonia recovered without their use. Fleischmann, at Vienna, declared that under infinitesimals the mortality from this disease only amounted to 5 per cent. of the cases treated. Dietl, at the Charity Hospital in the same town, found that whilst 20 per cent. died under treatment by bleeding or large doses of antimony, only 7 per cent. died when he trusted to diet alone and gave no medicine. And Hughes Bennett, at Edinburgh, who adopted a restorative treatment and abstained from bleeding, antimony, and the like, but gave salines and occasionally sweet spirit of nitre or small doses of colchicum wine, lost only 3·1 per cent. during a period of sixteen years over which his experience of this kind of treatment extended. I do not bring forward these figures as a proof that the mortality of pneumonia, apart from active medication, is as low as they would indicate. There are some sources of fallacy connected with these statistics which, however, I need not stop here to point out. But the observations on which the statistics were founded, and others to which they have led, have taught us that when inflammation of the lung has run a course of from two to ten days, it subsides in a large majority of cases, recovery occurring without the aid of drugs; and that the views held in former days as to the necessary dependence of recovery on early bleeding, though founded on the experience of able men, were fallacious. Want of knowledge of the natural history of disease led to an error in judgment.

During the last half century much information has been obtained as to the changes which occur in ailments not subjected to medicinal treatment; but our knowledge of the natural history of disease must be much more extended and minute than it is, before reliance on experience ceases to be delusive. There can be no doubt that we yet constantly attribute to medicines results which have no more connection with them than the recovery of the subject of Davy's experiment had with the thermometer; nay even less, for the thermometer was the mechanical agent of a mental influence, whilst a drug may not even play that *rôle* in the sequence of events which follows its administration.

It is to the acquirement of a knowledge of the natural history of disease that we must mainly look for making experience reliable, but this knowledge is more difficult to acquire than might at first sight appear. Only by minute observation of a large number of cases, which run their course in whole or in part without drug treatment, can we obtain it. But to withhold a drug which we believe would be useful in any single instance is as much an experiment as to give a drug the effects of which are unknown, instead of one which we think will cure, and we have no right, we feel, to jeopardise the life or comfort of our patients.

Here is a difficulty. Our duty towards our patients forbids experiment, for want of which experience often proves fallacious. It seems to me that in this dilemma two duties devolve upon us as medical men. First, we ought to put on record all minutely-watched cases which illustrate the course and phases of disease when uninfluenced by medicine. Such cases happen to all of us from time to time, and it cannot be too strongly urged that good reports of the natural history of disease are quite as valuable, nay, often more so, than the records of successful treatment by drugs. Superficial accounts or mere statistics of recoveries without the aid of medicine are not of much use. They add but little to the information we already possess. We want intelligent observations of *all* the facts relating to the phases through which disease passes when not influenced by medicines.

Secondly, we ought to enlighten the public more fully than we do as to the part which drugs really play in the treatment of disease. At the present time our course of action is influenced not only by our desire to do all we can for the cure or relief of our patient, but also sometimes by the fear that if we abstain from giving drugs our patients may lose that confidence which plays at times no unimportant part in recovery. And we are too apt to plead guilty to the soft impeachment of curing our patient with drugs which we are by no means sure had anything to do with return to health. If the public were better instructed in the exact position which drugs play in therapeutics, the action of medical men would be more unfettered, and we might soon obtain information we now lack. It seems to me, too, that another gain would follow—the public would be less easily deluded by the impudent claims of the quacks who so abound. As long as every success which follows the administration of a drug is claimed as due to the drug, so long will the public believe that the recoveries, which must from the very nature of things often ensue on the administration of quack nostrums, are a consequence of this administration.

Even when we are correct in the opinion that a drug has done good in a case, or series of cases, we cannot rely on its being of service in a new instance unless we know that the conditions are essentially the same as, or similar to, those in the other case or cases. Exactly the same thing can never be, for two cases never do present a collocation of symptoms in exact agreement, and similarity will not suffice if it refers to superficial resemblance only. The similarity must extend to all essential conditions, and in these essential conditions the pathological basis of the disease plays a very important part.

Manifestly we must not rely on the names by which groups of symptoms are known as guides to treatment on the ground of experience, for the same name may indicate ailments varying greatly in pathological conditions. And even when the name does connote the lesion, the similarity may not be sufficient to indicate that all instances of disease owning the same name will be similarly affected by the same treatment.

The remedy which saves life in one case of pneumonia may perhaps sacrifice it in another. The clinical history as well as the morbid tissue-change in two cases must be similar before experience in the one case can guide us aright in the treatment of the other.

The more intimate our knowledge of pathological changes, the more minute our clinical observation, the truer will be our judgments as to real likeness, and the more successful our reliance on experience as a guide to the selection of a drug in cases of disease. Let me here then enter my protest against the cavils of those who hold that too much attention is being given to pathology and diagnosis, too little to therapeutics. Experience, which I maintain is after all the firmest basis for treatment by drugs, is essentially dependent on pathology and clinical knowledge.

But experience can only avail when we meet with cases truly similar to those which have been treated by ourselves or others. As soon as ailments come before us of which we have not met the like before, we are guided in drug treatment by a train of reasoning, never devoid of one assumption, often involving several.

Those who maintain that they act only empirically make an idle boast; they use hypotheses, but as M. Jourdain talked prose—without knowing it; for the phases of disease are so various that everyone must frequently be meeting with cases differing in some respects from any he has seen or known before, and some hypothesis with regard to curative action precedes every new application of a drug and the use of every new drug for the cure of disease. Our so-called empirical remedies have for the most part been first employed on hypotheses now discarded. The value of a few may have been discovered by accident. But no man gives a drug on pure chance, though he sometimes thinks he does. Equally mistaken, it seems to me, are those who believe that in the absence of experience they proceed according to therapeutic laws, that is, if by the term "laws" are meant general laws or laws of nature, which are universally true whenever they are applicable, such as the laws of gravity in physics, and of combining proportions in chemistry.

We have at present, I contend, in therapeutics no general laws, but only approximate generalisations, or empirical laws which cannot be certainly relied on beyond the conditions in which they have been confirmed by actual observation. When experience fails us I hold we always use these, conjoined with hypotheses more or less probable, by means of which we are led to consider some plan of treatment most likely to succeed; and should this plan of treatment prove really successful, we have an addition made to the sum total of our experience.

Now there are two ways in which hypothesis may be used. We may imagine a general therapeutic law or laws, and thence make deductions as to the use of a drug in a particular case, or having established by observation certain approximate generalisations or empirical laws, we may, if experience fails us, assume that the instance before us comes under one of these generalisations or laws, and on this assumption make trial of a plan of treatment in accordance therewith. As our trials in either case are founded on a deduction of which a hypothesis forms either the major or minor premiss, our results can never be absolutely assured.

Hence the uncertainty of much of our medical treatment, and hence it is that experience, delusive though it often is, is rightly looked on as the surest basis of medical treatment. Of necessity, indeed, we most frequently found our therapeutic procedures on deductions; but we ought to look upon such procedures only as leading to experiments which are the more likely to succeed as the hypothesis involved in the deduction is the nearer to truth.

A large proportion of the therapeutic errors of past ages, and some of those of the present time, have arisen from the acceptance of hypotheses as general laws. Because it could be shown that many of the deductions from these hypotheses were correct, the correctness of the hypotheses themselves was considered proved.

Now it is quite evident that false hypotheses may readily lead to deductions in accordance with actual experience. Take, for example, that absurd hypothetical law known as the doctrine of signatures, which was upheld by Paracelsus. According to this doctrine, the external characters of a plant indicate the ailments in which it will be found useful.

Yellow plants, it was taught, cured yellow diseases. Plants with a head like the poppy cured head affection. It is evident that, absurd as such a doctrine is, it might lead to new therapeutic knowledge. It may have led, for example, to the use of the inspissated juice of the poppy head (opium) in certain head affections, in which it is really of service. It probably did lead to the juice of the celandine being tried in some liver affections with advantage. By suggesting experiment even this hypothesis perhaps served a useful purpose in the dark ages in which it was promulgated. But though these effects of opium and celandine might then have been deduced from the doctrine of signatures, this would not show that the doctrine was a law.

The acceptance of a hypothesis for a law biases the judgment as to the result of experiments to which it leads. Where judgment is difficult we are apt to think we see that which we think we ought to see. The firm belief in the efficacy of the most divers systems of treatment in past times seems to me chiefly due to the biased judgment which has followed the acceptance of theories as laws, and the more firmly, as a rule, theories have been held as laws, the less has been the true progress of therapeutics.

Hippocrates, who added greatly to the knowledge of medicine and general therapeutics, if not of drugs, held groundless theories of disease. He thought the four elements of earth, air, fire, and water, of which, according to him, the body consisted, produced the four humours—blood, phlegm, bile, and black bile. But he does not seem to have let these theories interfere materially with his observations of the course of nature or the effects of treatment, and hence the great additions which he made to real knowledge. He was content to watch and record.

The treatment of disease by superstitious rites, by charms and amulets, so prevalent in early times, was really based on hypotheses, more or less definite as to the cure of disease, originating in others relating to its causation.

Unable to understand the nature, and therefore the cause, of disease, the impressionable minds of older days seized on the agencies which most attracted their attention, and imagined them as causes. To their gods, to evil spirits, to the stars, the outbreak of pestilences and ailments of all kinds was attributed. Astral influence has indeed maintained its credit till a comparatively recent date. "One cause of breeding of the pestilence," says an author of the time of Charles the Second, speaking of the plague, "is that corruption of the air which is occasioned by the aspects and conjunctions and oppositions of the planets, and by the eclipses of the sun and moon." I am not sure whether this belief in the influence of the stars has even yet quite died out. Hypotheses of causation once believed in, treatment on the same lines followed as a matter of course. In very early days superstitious rites were employed to arrest pestilence, and, afterwards, measures thought likely to propitiate evil spirits or destroy their power.

In amulets, charms, and precious stones were supposed to reside good spirits, which checked the action of the bad, and since patients who wore these amulets and charms often got better from diseases, the value of the charm and the truth of the spirit theory were considered to be proved. Since, too, the causes of diseases had an obscure and mysterious origin it seemed that the means of cure must also be mysterious, and on this slender hypothesis was founded treatment consisting of mysterious concoctions into which entered roast toad, moss out of the charnel-house skull, and many other uncanny and nasty things.

Again, if, as was believed, stars influenced disease, what more likely than that they should also influence plants used to cure disease. On this hypothesis we have the astrological herbals in which full directions are given as to the starry or lunar influence under which each herb must be gathered to have its full healing influence. It became usual to precede receipts by a symbol of the planet under whose reign the ingredients were to be collected. The letter R, which commences our prescriptions, is the relict of the astrological symbol of Jupiter.

If hypotheses such as these could lead, as they doubtless did, to the acquirement of some true facts by the trials they induced, it is not to be wondered at that guesses at truth of greater probability should have added to our real knowledge. And so they did. Yet in one way they were more prejudicial to true progress; for the more attractive the hypothesis, the more firmly was it believed in as law, the more therefore did it bias judgment.

The doctrine of Themison and the Methodists that all diseases were due to constriction or relaxation of the pores of the animal tissues—and therefore that all medicines were relaxants or astringents—the doctrine of Galen as to hot and cold, dry and moist remedies, and several others of the same kind, for this reason rather fettered than aided the progress of therapeutics, and the same may be said of the mechanical and chemical theories which have reflected the prevailing turns and tides of thought. As time has gone on, and the laws of the human frame have become better known, medical hypotheses have for the most part become less fanciful and more in accordance with the observed course of nature, but the fatal error of regarding them as laws of practice, not as theories which should lead to unbiased experiment, has ever been the cause of evil; and the theories of Stahl, and Brown, and Broussais, instead of leading, as they might have done, to real advance in therapeutics, have only led to waves of varying practice, concerning which it is not quite easy to say which was the most futile.

The doctrine of *similia similibus curantur* is a signal example of the error made in confounding a hypothesis with a law of nature. Long before the time of Hahnemann, it had been noted that medicines did good in some diseases, the symptoms of which were like those produced by the medicine. And some writers had even speculated whether there might not be some law such as that which Hahnemann afterwards formulated; thus Störck, in his book on Stramonium, Hyoscyamus, Aconite, and Colchicum, published in 1762, says: "Interim tamen ex his formavi sequentem quæstionem. Si stramonium turbando mentem adfert insaniam sanis, an non licet experiri, num insanientibus et mente captis turbando, mutandoque ideas, et sensorium commune adferret mentem sanam, et convulsis tolleret contrario motu convulsiones." He gives an experiment which seems to favour this idea.

Hahnemann, however, was the first to maintain that *similia similibus curantur* was a, or rather *the* general law of therapeutics—a law of nature. Here was his great error, though there can be no doubt that his success in founding a sect was due to the error. His hypothesis was much more superficial in character than several of the theories which had preceded it, but it was wider in its scope and more easily adapted as a guide to practice.

It could readily be shown too, that many deductions drawn from it were in accordance with known facts, and the indefinite extensibility of the term "like" rendered it possible to use the law in explanation of many phenomena connected with the treatment of disease which were not at that time understood. Promulgated as a theory, or one of the theories of the action of medicines, it might have attracted many, and would probably have repelled few; but its acceptance could only have been of short duration, for, as a general law, it was wanting in the precision which the medical knowledge of the time demanded. But when Hahnemann, vehemently insisting that it was a law of nature, built upon it a system of practice, though the majority refused to accept either law or practice, a few were strongly attracted by the simplicity of the one and the apparent success of the other. Enthusiasm and strong belief, the tendency of disease to spontaneous cure, and injudicious persecution, aided Hahnemann and his immediate followers in establishing a distinct medical sect. The bias which the acceptance of a hypothesis for a general law gives in the estimation of the results of experiment has probably never been better illustrated than in the case of homœopathy. Few I take it now look on *similia similibus* in the light that Hahnemann did, as an ultimate law of nature. It has long been manifest that the word "like" can never be the pivot on which a general law turns, though some still regard *similia similibus* as an approximate generalisation useful as a guide in treatment. The continuation of a system of practice for some time after the law on which it was originated has been found untenable is only what has been observed in all cases where a system of practice has been built on an erroneous theory. Let me point out here, however, that, as real discoveries may, as I have shown, result from experiments made on absolutely false hypotheses, so it is a mistake to throw doubts on curative actions simply because they have been discovered on the ground of the hypothesis *similia similibus.*

The theory of *contraria contrariis,* I need hardly say, has no more right to be considered a law of nature than *similia similibus,* and no one, I suppose, now thinks of founding upon it his principles of treatment.

In the therapeutic procedures of the present time, in so-called rational therapeutics, we do not profess to depend on any wide general law relating to cure. We are led to the choice of a drug by previous experience of its utility in cases essentially similar. Experience failing to provide us with such cases, we are guided either by analogy, or by our knowledge of the effects of drugs and disease on the structure and functions of the body, and by approximate generalisations as to the course of disease founded on observation; but, as we are unacquainted with the limits within which these generalisations are true, we have to *assume* that the case before us falls within these limits.

Acting on this assumption, we make trial of a drug; the more correct our hypothesis the greater the probability that the trial will be successful, provided always that our knowledge of the effect of drug and disease is correct.

Let me illustrate this. In a case of severe typhoid fever with weak action of the heart, we are guided to the selection of a drug—say alcohol, in the first place by our knowledge of the condition of the organs. We may know, for example, from the pulse and the condition of the first sound of the heart, that this organ is in a failing condition, whilst other organs show no signs of giving way. In the second place we depend on our knowledge of the action of alcohol as a cardiac stimulant. But, thirdly, we act in accordance with an approximate generalisation. Observation has taught us that in an ordinary case of typhoid fever recovery takes place, provided the heart's action does not fail. We are perfectly aware this is only an approximate generalisation. It is not always true. Death may take place apart from heart failure, owing to lung or intestinal affections; but we act on the hypothesis that the case before us belongs to that class in which recovery takes place if the heart does not fail, and we give alcohol. Provided our knowledge of the condition of the organs and the effect of the alcohol is correct, our success will depend on the correctness of our hypothesis.

In the use of antipyretics again, we often employ the generalisation, also founded on observation, that recovery takes place if the temperature can be kept down. Manifestly this is only an approximation to the truth; we know full well that many cases die even though the temperature never rises unduly high; but in every individual case where we employ antipyretics, we act on the hypothesis that it belongs to that class which will recover, provided the temperature remains within certain bounds, and our success depends on the validity of this assumption.

It will be observed that both the above-named generalisations are founded on a wider one, that in diseased conditions there is naturally a tendency to a return to health.

Another approximate truth founded on observation which we largely employ, is the statement that, if the cause of a disease be removed, recovery will follow. If the word cause were used in its strict sense, as the sum total of the immediate and necessary antecedents, this statement would come under a general law which is universally true. But in the loose way in which the word cause is used in relation to disease, the generalisation is only true within certain limits, and a hypothesis of more or less probability is involved when we employ it as a means of arriving by deduction at the remedy required in an instance of disease.

If, for example, a man should come before us suffering from violent pain and nausea after a hearty meal of pork, and we feel satisfied that the pork has been the exciting cause of the trouble, we may give an emetic on the assumption that the case belongs to that class of ailments in which, on the removal of the cause, recovery takes place. Here, again, if our view of diseased condition and drug action be correct, if the stomach is really overloaded by undigested pork which has set up irritation, and if the emetic acting according to a pharmacological law causes its ejection, the experiment will be successful, provided our hypothesis be correct that the case belongs to the class in which the removal of the apparent cause is followed by recovery. In the example before us, the assumption is made with very great probability, but it is not necessarily correct. The pork may be there, it may have originated the trouble; the emetic may act according to law, yet it may fail to relieve. We often proceed on the supposition that the principle "tolle causam" holds good in ailments which are only doubtfully within the limits of its application. In the case of paralysis known to be caused by the poison of specific disease, and with the certainty that iodide of potassium or mercury will remove the poison, we may nevertheless be uncertain whether we can rightly assume that removing the cause will cure the ailment; for whilst the originating poison may be removable the sequential changes in some part of the nervous system may be unalterable by medicaments. It may be contended that in this and similar cases the conclusions may be invalid, not because we conclude erroneously that our case comes under a partial generalisation, but because we assume falsely that the poison of specific disease caused the paralysis, which was really due to certain tissue changes induced by the poison; or, in other words, because to a general law as a major premiss we tack on a hypothetical, and in this case erroneous, minor, such as: "The poison of specific disease caused paralysis." This is true if the word cause be only used in its strict sense. But in the absence of definite knowledge concerning any other immediate and necessary antecedent, we usually look upon the most distinct originating influence as the cause of a disease; and it is by the removal of this influence that in practice we count on accomplishing cure. It is in this sense that we often look upon certain materials present in the intestinal canal, blood, or tissues as causes of disease, and employ evacuants to get rid of them. On the belief that a certain material present in some part of the body causes the ailment before us, we give whatsoever drug pharmacological knowledge teaches us will expel this material.

Removal of "peccant material," when we can accomplish it, usually relieves or cures. It is by no means certainly successful; yet we constantly give drugs, as if such removal must be so.

A third generalisation of uncertain limits, allied to that relating to the removal of cause, is not unfrequently employed in therapeutic reasoning. Disease is a deviation from the normal state of some of the functions and tissues of the body. Cure consists in a restoration to a normal state of all these functions and tissues. It does not follow, however, that a drug which effects the restoration of one of them to the state it was in during health will cure; such restoration may indeed lead to further troubles. The return of the skin to a normal state in some eruptive diseases is followed by great evils, yet we know that often, when several organs are affected, the restoration of one of them to a healthy state is followed by the return of all, so often indeed that we act as if this were a general principle. In a case of cardiac disease for example, with bronchitis, anasarca, ascites, anorexia, nausea, and enlarged liver, we often give digitalis, for we know that if we can influence the heart, and make it act as in health, cure, or at least the return of all other organs and tissues to a state approaching recovery as near as possible, will follow. Here, indeed, we can well understand why this should be. Often we see but dimly the relationship between the alterations in function and tissue of various organs which together constitute a condition of disease, and sometimes this relationship is quite hidden from us. Nevertheless, even then, in default of a better indication, we try to restore the healthy function of the organ most prominently affected. Now, whenever we select a drug with the idea that the restoration of one organ to its normal state will be followed by the return of all, we act on the supposition that our case belongs to the class in which such a general return does follow. If the supposition be correct, the drug will bring about the result we desire, provided, of course, that our view as to the condition of the organ we have to influence by the drug be true, and our idea of the effect of the drug be correct.

It seems to me that in all therapeutic reasoning relating to cure, we use one of the approximate generalisations just indicated, or at least one of a similar kind, and the consideration of the nature of the case before us indicates the one we may most profitably employ. Having decided upon it, and assumed that the case before us comes under it, we next atempt to influence certain functions or tissues in accordance with it, and the relation of pharmacology to therapeutics consists in this, that a knowledge of the physiological action of drugs teaches us how we may thus influence those functions and tissues in the direction which, according to our generalisation, is most likely to lead to a return to health. From pharmacological laws we learn how we can so sustain an organ as to prevent an early loss of function; how we can so act on an emunctory as to cause it to carry off either an excess of the material which it naturally excretes, or material which is foreign to it; how we can stimulate an inactive organ, or depress the undue activity of an organ; how we can increase, decrease, or alter the nutrition of a tissue.

Of course our knowledge of the effects of drugs on functions or tissues can only be effectually employed when we know the conditions to which they have been brought by disease, and therefore the data of therapeutic reasoning may be said to be:—

(1) Approximate generalisations relating to the cause or course of disease.
(2) A knowledge of the effects of disease on the various functions and tissues.
(3) A knowledge of the effects of drugs on these functions and tissues.

In the trains of reasoning used in what are called rational therapeutics all these data are commonly employed, but under some conditions they are not all needed for the determination of treatment. When, for example, we desire simply to alleviate pain, we may use the empirical laws relating to the physiological action of drugs without the aid of generalisations concerning the course and cause of disease. We may thus employ the law that chloroform annuls sensation. It may be noted, however, that if we relieve pain to promote restoration to health, we at once use a generalisation only partially true, that relief of pain tends to recovery, and assume that the case before us comes under it.

Again, we not infrequently use approximate therapeutic generalisations in place of pharmacological laws. In a case of typhoid fever, for example, with severe bronchitis, having assumed that it belongs to that class which will get better if bronchitis be subdued, we may act upon the proposition that a certain drug cures bronchitis instead of considering the special lung functions we ought to influence. But in using these general therapeutic propositions, founded on experience, we generally have likewise a hazy idea of certain pharmacological laws from which they might be explained, and the less we can explain them, the less can we rely upon them. We very constantly, as I have said, thus combine reasoning founded on hypothesis and experience.

It will be observed that I make a distinction between the generalisations of pharmacology and therapeutics. I believe there is an important and essential difference between them.

Therapeutic generalisations are founded necessarily on the methods of agreement, and hence they must ever be insusceptible of the exactness which is possible when other methods of investigation can be employed. However many recover from an ailment under the action of a certain drug, we can never be sure that every one will do so. As we cannot find naturally, nor produce by artificial means, cases of disease so exactly similar that we can be sure they will pursue a uniform course unless a disturbing influence such as a drug be introduced, we cannot determine accurately the influence of the drug on the general course of disease in any individual case. Our generalisations as to the therapeutic effects of drugs must therefore be always more or less approximate. On the other hand, in pharmacology we can often employ the method of difference and can therefore arrive with certainty at laws, empirical indeed, but reliable within limits capable of being fairly well defined; for the functions of the organs and tissues of the body are performed with such regularity in healthy animals that we can safely look upon the effects which follow the introduction of a disturbing influence such as a drug as the cause of the differences which follow. We can therefore often ascertain definitely the effects of drugs, that is the law of their action. The effects of atropine on the vagus and of nitrite of amyl on the pulse, for example, are absolutely reliable within limits which can be defined. It is true that exact knowledge is at present confined within narrow bounds, and that we are in doubt as to the exact effect of many drugs on healthy organs. Nevertheless pharmacological laws are the most reliable of the data we use in therapeutic deductions. Herein lies their value. But to use them aright we must always be fully alive to the narrowness of the limits within which we can trust their application, to the fallacies natural to observations on the physiological action of drugs. Let me briefly point out some of the circumstances which thus limit us and lead to errors in our deductions.

Though we can be sure in any individual animal that a drug will act on a function in a definite manner, we are in no new instance certain as to the quantity which will be required to produce this action. The same dose of alcohol may be taken by two men: in one no effects can be perceived; in another, from its action on the brain, very definite phenomena follow. It has long been known, too, that a large number of drugs possess what is called a double action, first stimulating then diminishing the activity of the functions on which they act. Opium, for example, first excites the brain, then causes sleep. Now this opposite action is largely dependent on the dose. The eighth of a grain may cause excitement with hardly any indications of drowsiness, whilst two grains given to the same man may quickly produce deep sleep with only very slight indication of excitement, or it may be none at all. And further, in two individuals in whom, so far as we can tell, all the functions of life are carried on in an exactly similar manner, the same dose may produce opposite effects; a grain of opium exciting one man and causing sleep in another.

The dose which first causes one effect will sometimes, if the administration be continued, lead to the directly opposite effect. Ten drops of tincture of digitalis will, after a few doses, make the pulse beat more slowly and more forcibly; after a few more doses it will make it beat quickly and with weakened power.

Sometimes, too, the dose of a drug which at first caused distinct effects on an organ, ceases after its continued exhibition to influence it.

Again the difficulties in deciding upon the part played by a drug in the results which follow its administration are often very great, the more so since much of our knowledge as to the effects of drugs on special functions is of necessity derived from experiments on animals, and we are not always assured that remedies affect the various organs of man and the lower animals in the same manner.

Now these limiting circumstances and sources of error interfere much with the utility of pharmacology as a guide to treatment; but though they must ever be borne in mind, they by no means abolish our reliance on pharmacology. For the variability of the effects of drugs on organs depends, as already indicated, not on the difference in kind of action, but on difference in susceptibility, and on the contrary action of varying doses. If we could judge of the susceptibility of an organ to a drug, we could count absolutely on always producing the same effect by modifying the dose in accordance with the susceptibility. Though we cannot do this, we often can, by modifying the amount of the dose, count with certainty on influencing the same organs, in different individuals, in the same direction by a drug.

With regard to the difference between the effects occasionally produced on organs at first, and after prolonged administration, we can ascertain by experience under what conditions this difference must be taken into account.

The difficulty of determining in some cases whether the effects which follow a drug are due to it or to other causes must ever remain, and we are at times compelled, in therapeutic reasoning, to assume the truth of pharmacological data which are doubtful. But the identity between the effects of remedies on functions and tissues in man and the lower animals can be established in many cases beyond all doubt, and when from difference in construction or other causes man is not affected by an agent in the same way as some of the lower animals, we, as a rule, readily become aware of this by experiment or observation. Pharmacological laws relating to man cannot, of course, be founded on facts observed only in the lower animals. Such facts can only indicate that similar phenomena probably will occur in man, and, if in therapeutic deductions we assume without proof that it does so occur, the correctness of our conclusion will be only in accordance with the correctness of our assumption.

Notwithstanding the narrow limitations within which alone we can employ pharmacological laws, these laws do often afford us firm data in our reasoning. But when applying these laws in therapeutic procedures we often make two assumptions which I must here notice. Firstly, that diseased functions and tissues are affected in the same manner as the healthy; and secondly, that when by means of drugs organs are so influenced as to return towards their normal state, they will not, on withdrawing the drug, revert to their former abnormal condition. In many instances we can ascertain by observation that the effects of a drug on a diseased and healthy organ are identical; we can even use experiment to determine this, for we can induce some pathological conditions artificially, and prove the effect of a drug as distinctly on the diseased as on the healthy organ.

Our belief, again, that the alterations in the functions of an organ produced by a drug will continue after the drug is withdrawn, is founded on an approximate generalisation. We note this continuance in so many cases that we look for its occurrence in all.

When, for example, digitalis has strengthened and rendered slow the action of the heart, and the dropsy and other symptoms which accompanied quick and weak cardiac action have gone, we ordinarily find that evil symptoms connected with the heart do not reappear when the drug is no longer given, at least not without some further cause; but yet we see occasionally this continuance of a more healthy state wanting without any satisfactory cause. Where we use the generalisation I am alluding to in reasoning, we can only assume with more or less probability that the case before us comes under it.

I have set forth at some length some of the numerous assumptions we are obliged to make in therapeutic reasoning, because it seems to me that evils have ensued from forgetfulness of the important part which hypotheses play therein. On the one hand, some seem to rely on their conclusions as if they used laws only in their deductions, and such men are too apt to see in their experiments that which they think they ought to see. Others, again, finding that their deductions so often fail, pass to the opposite extreme and lose faith in all attempts to treat disease rationally. There are, indeed, many sources of fallacy in our reasoning, but we have now therapeutic generalisations so nearly approaching laws, and pharmacological laws of such certainty, that in many cases we can depend with fair confidence on the conclusions deduced therefrom.

It is probable, too, that careful observation will enable us to render our therapeutic generalisations still further akin to laws; but it is to pharmacology that we must look for the greatest advances, for here we are beginning to see, dimly though it may be, the nature of the general laws, by which our present empirical laws relating to the action of drugs may be explained.

Even now it is perhaps right to look upon the proposition enunciated some time ago by Dr. Rabagliati,[1] "Different remedies tend to act on different parts of the human body," as a law of nature. I am hardly, however, inclined to regard in the same light his second proposition, "The secondary action of any and all acting remedies is contrary to the primary." It seems to me that at the present time all we can assert with confidence is that *most* remedies have opposite effects in different doses. We may hope before long to explain the cause of the selective action of drugs, of the different effects of different doses in the same individual, and of the same dose in different individuals, by showing that they depend on other laws of wider generality. Already hypothetical laws have been put forth for this purpose by Dr. Headland, Dr. Rabagliati, Dr. Ross, and others, some of which may prove to be real general laws, or may lead us to discovery of such laws. When these are established, we may expect that the progress of therapeutics will be rapid, but meanwhile we must beware of accepting for laws governing practical procedures, theories, or approximate generalisations. Nothing in times past has been more fatal to real progress in the therapeutic art. As long as we use them with a full appreciation of their exact nature no harm accrues, nay often good. The application of our knowledge of the frequency with which medicines produce contrary effects in different doses often indicates new uses to which we may put them. The theory of the action and reaction following on their administration explains failures and successes which otherwise would puzzle us, and leads to new experiments. But in the treatment of disease it would be a mistake as yet to rely absolutely on the existence of a double action in the case of every drug, or to look for the invariable appearance of reaction.

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[1] "Practitioner," vol. xix., p 169.

Thus far I have only alluded to two methods by which we are guided in selecting a drug, experience and the deductive method which I have described at length; analogy may be looked upon as a third. When, casting round for a remedy in an instance of disease, we meet with no exact counterpart, we sometimes call to mind another case like, yet we are aware not *essentially* like, the one before us, and try the same remedy which succeeded there. We proceed on the assumption that the two cases, though not quite similar, may be affected similarly by the same agent, or that the presence or absence of certain symptoms by which the two cases differ will not invalidate the action of the remedy. Here manifestly our experiment is founded on a hypothesis, and success will depend on its correctness.

In the earlier portion of this lecture I stated my opinion that experience, notwithstanding all its possible fallacies, is the firmest basis for therapeutic procedures. I think I have shown that in the present state of our knowledge there is good reason for this view. The consideration that a remedy has restored health in a case or cases essentially like one before us must ever outweigh conclusions derived deductively in either of the two ways I have indicated.

Our views as to treatment are often formed partly on experience, partly on reasoning, but sometimes reasoning and experience clash instead of coinciding; when this is the case we, as a rule, acknowledge experience to be the best guide by trusting to it, and with good reason. When the value of mercurial purgatives in certain affections of the liver seemed disproved by the investigations of Bennett and Rutherford, who showed that mercury did not increase the secretion of bile, it was concluded that experience and reasoning were opposed. It is now, I think, generally acknowledged that they who continued to rely on experience acted wisely; the deduction that mercury could not be useful because it could not be shown to increase the flow of bile was founded on an erroneous assumption, that in these affections stimulation of the liver secretion was necessary to the cure. Undoubtedly experience is deceptive, and if we could feel assured that the data of our therapeutic deductions were reliable we should trust to these deductions rather than experience. But it is not so. In our reasoning we are compelled to use assumptions and observations, both of which may be erroneous.

A time may come when increased knowledge of the laws of pharmacology and disease may enable us to formulate therapeutic laws as certain and as wide as those of chemistry, but much, very much, has to be done before this can be accomplished; and considering the difficulties of precise investigation, where life is concerned, it seems to me no disgrace to the medical profession that more generalisations cannot be made as yet. Until they are made medical men must ever remember the pitfalls into which they may be led if they do not fully appreciate the uncertainties surrounding their judgments, owing to the uncertainty of the data on which they are often of necessity founded. They must ever bear in mind, on the one hand, the fallacies, special to experience, arising from imperfect observation and bias; on the other, those which may be due to false hypotheses. As long as we remember these things, we shall constantly look out for errors and shall be chary in our decisions, but if we forget them, or mistake a hypothesis for a law, undue reliance on our conclusions will tend to land us in a fool's paradise.

SPIRITUS ÆTHERIS NITROSI.

1883.

Spirit of nitrous ether has been administered as a medicine for several hundred years. A preparation of it was given medicinally as early as the thirteenth century, and since the fifteenth century, when Basil Valentine introduced an improved method of preparing it, the spirit has been very largely used. In England especially it has been much employed, and though at the present time held in less repute than formerly by the profession, its use as a domestic remedy under the name of "sweet spirit of nitre" is common throughout the land. But if we turn to what has been written concerning the physiological action of this drug, we find the information given to be but scanty. Dr. Garrod calls it a stimulant diaphoretic and diuretic, and a refrigerant. He states, too, that it increases the water whilst diminishing the solids of the urine. Some French authorities, as Trousseau and Pidoux and Rabuteau, following Flourens, classify it with the anæsthetics, whilst Dr. Richardson denies that it possesses anæsthetic power. Both Simpson and Snow, however, found it induce insensibility to pain. Wood, after pointing out that its inhalation may produce poisonous effects, says that in ordinary doses it exerts no marked effects beyond increasing the action of the kidneys and skin, but he considers it may act as a stimulant to the nervous system, and in the same manner as antispasmodics do. Pareira, too, speaks of it as a carminative. It has also been alluded to by some authors as a cardiac, and likewise, too, as a diffusible stimulant. Dr. Ringer apparently thinks it is a drug unworthy of consideration, as he does not even mention it in his handbook; and many other writers seem to doubt its value as a therapeutic agent. Some experiments, however, which I have recently made with the pharmaceutical preparation, lead me to believe that its physiological effects are by no means slight, and that a knowledge of them may lead us to a better comprehension of the mode of action and true value of the drug than we have hitherto had.

Spirit of nitrous ether, even in ordinary doses, is a distinct depressor of arterial tension. Its properties depend, of course, on the nitrous ether it contains, and these properties are like to those which nitrite of amyl, nitro-glycerine, and the nitrites of the alkaline metals have been shown to possess; but, contrary to what might have been expected, the influence of the drug upon the circulation is of considerable duration.

The fact that nitrite of ethyl is capable of influencing the circulatory organs in the same manner as nitrite of amyl was first pointed out by Dr. Richardson in 1867, though Hermbstädt had previously noticed that the vapour of nitrous ether affected the head and caused fulness of its vessels.[1] Richardson found that in man it caused a sense of fulness in the head, rapid action of the heart, and suffusion of the skin, just as nitrite of amyl does, and that, like this latter drug, it causes the blood to become of a chocolate colour. Dr. Hay, in his recent papers in *The Practitioner*, "On the Value of some Nitric, Nitrous, and Nitro-Compounds in Angina Pectoris," confirms Dr. Richardson's statements. He proves that nitrite of ethyl further resembles nitrite of amyl and the other nitrites, in its power of averting anginal attacks, but he states that twenty minims of a solution of the nitrite in alcohol produced on himself no perceptible effect, and that given to a patient with angina it also failed to produce any effect on the ailment till sixty or seventy minims had been taken; then it acted like nitrite of soda.[1]

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[1] Strumpf Arzneimittellehre, vol. i., p. 1014.

Dr. Hay's experiments led me to try the spirit. æth. nitr. of the pharmacopœia, which probably contains, when pure, from three to four per cent. of nitrite of ethyl.[2] I find that if 100 minims of spiritus ætheris nitrosi be given to a healthy subject, the sphygmographic pulse-tracing invariably indicates a marked fall in arterial tension, and that this decreased tension lasts for two or three hours. I find, too, that smaller doses, such as fifty or twenty-five minims, produce a similar influence on the circulation, though it is less marked and less enduring. Increased frequency of beat always accompanies the fall in tension, and the percussion wave in the tracing is heightened.

The tracings (Figs. 1—7) show the results of 100 minims of spiritus ætheris nitrosi, on V. C., a man aged 30, somewhat debilitated, but with sound organs.

The spirit used was obtained from Messrs. Woolley, Sons and Co., and was found to effervesce rather strongly with bicarbonate of soda, but to be otherwise free from impurities, and to answer to the pharmacopœial test of strength, that is, it threw up two per cent. of an ether when treated with saturated solution of chloride of calcium. It contained but little aldehyde.

It will be noticed that one-and-a-half minutes after the spirit was taken its effect on the pulse was not perceptible, but that in three minutes it was marked, and in eight minutes the tension was very low. In thirty minutes a slight rise occurred, and this gradually became more distinct for some time. Rather more than an hour after the ingestion of the drug a fall in tension occurred—this is well seen in the tracing Fig. 6 taken at eighty minutes. After this, succeding pulse-tracings showed a gradual rise, but in three and three-quarter hours the pulse had hardly reached its normal tension.

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[1] The solution, though supposed at the time it was used to contain 25 per cent. of nitrite of ethyl, was afterwards found to contain only 1½ per cent.

[2] It is usually supposed that the separation of 2 per cent. of an ethereal liquid on the addition of calcium chloride to spirit. æth. nitr. indicates the presence of 10 per cent. of nitrite of ethyl. Dr. Dupré, however, in a paper published in the *Pharmaceutical Journal*, August 2, 1879, says that spirit. æth. nitr., prepared by the B.P. process and answering to the B.P. test, may only contain 3 per cent. of nitrite of ethyl.

In all the instances in which I have determined the effects of spirit of nitrous ether on the circulation, I have observed like results, but the effects have not been usually so long-lasting as in this case. V. C., though otherwise healthy, was weak from the results of bowel catarrh, and his circulation was somewhat readily influenced by drugs as well as by excitement.

In order to ascertain whether the rectified spirit which forms so large a proportion of the sweet spirit of nitre had any share in the production of the effects above noted, we administered on the day following 100 minims of spt. vini. rect. to the same man, and my House Physician, Mr. Harvey Jones, to whom I am much indebted for aid, took a series of tracings which proved that this quantity of spirit did not influence at all the tension of the pulse.

The tracings (Figs. 8—14) show the effects of spiritus ætheris nitrosi on the pulse of V. C. in doses of fifty and twenty-five minims, some days afterwards.

It will be seen that an hour after fifty minims the tension was not fully restored. I have seen the effect of the drug in this dose perceptible for 150 minutes, whilst twenty-five minims will at times affect the pulse for eighty minutes.

The duration of the influence recognisable by the sphygmograph depends on the condition of the circulation, and hence varies somewhat in different individuals. It varies, too, to a certain extent in different individuals at different times. V. C. took the nitrous ether on many occasions; only once after taking 100 minims did he complain of slight throbbing in the head and giddiness. On another occasion, when the tension was at the lowest, he broke out into a profuse perspiration. After the smaller doses he felt no effects.

The tracings (Figs 15—18) were taken from the pulse of Mr. Evans, one of our House Physicians at the Manchester Royal Infirmary, after the administration of 100 minims of spiritus ætheris nitrosi. I may say that the clockwork of the instrument used has a quicker rate of speed than that employed in the case of V. C.

Save for slight eructations of nitrous gas Mr. Evans says he felt no results from the dose he took. As a rule, indeed, the administration of ʒj. to ʒiss. of spirit of nitrous ether is not followed by any distinct alterations in the feelings indicative of the effect on the pulse which is invariably produced. This absence of subjective symptoms, when the circulation is so evidently influenced, is worthy of note.

Sometimes, however, a full dose of the spirit causes a slight feeling of faintness and depression. I have myself experienced this, and can call to mind instances in which patients have complained of similar effects. A medical friend of mine informs me that even moderate doses invariably influence him in this manner.

The tracings show that an increased pulse-rate always accompanies the decreased tension, but I have not yet satisfied myself as to the exact relation between rate and tension at various periods. The frequency of the heart-beat appears not to be increased so markedly as by nitrite of amyl and nitro-glycerine; and indeed at times, especially when small doses are given, the accelerating effect is very small.

I shall not here discuss the precise manner in which spirit of nitrous ether produces its effects on the circulation. Its action is evidently analogous to that of nitrite of amyl, nitro-glycerine, and the other nitrites, and it probably influences the same tissues.

I have never seen proof of its effects on the central nervous system apart from those dependent on the circulatory changes which it induces. In large doses the spirit with which the ether is associated may lead to the antispasmodic and carminative action alluded to by Wood and Pareira; but the ether in itself has probably some influence, for there are indications that in some people at least it affects the muscular walls of the stomach and intestines.[1] It is quite possible, too, that in very large doses it may be found to depress the motor functions of the cord like amyl nitrite.

The therapeutic *rôle* of spirit of sweet nitre seems chiefly due to its influence on the circulation; and a consideration of the manner in which this influence is exercised will, I think, enable us to understand better than heretofore its failures and its successes as a remedy.

Spiritus ætheris nitrosi has chiefly been used for its diuretic and diaphoretic properties; but it is described as a febrifuge by many writers, and is a common ingredient of fever mixtures. It is by virtue of its tension-reducing effect I think, by its power of dilating the arterioles in certain parts, that spiritus ætheris nitrosi acts as a diuretic. It seems probable that any agent which increases the rapidity of the blood-flow through the vessels constituting the Malpighian glomerulus is capable of increasing the secretion of water, and that both those which raise arterial tension and those which decrease it may, under different conditions of the circulation, in this way promote diuresis. Dr. Murrell's experiments with nitro-glycerine in a case of epispadias[2] distinctly prove that this drug is capable of temporarily increasing the urine flow, and the relation there evidently is between the effects on the circulation it usually produces and the increased secretion of urine noted by Dr. Murrell leads me to the conclusion that its diuretic action is dependent on its circulatory influence. Nitrous ether closely resembles nitro-glycerine in its physiological effects on the circulation; and in the absence of any facts tending to prove that nitrous ether stimulates the kidney secreting structures specially, we may fairly conclude that the diuretic properties of sweet spirit of nitre depend on its influence on the circulation.

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[1] Kraus notes colic and vomiting as present in a boy who took ʒj of nitrous ether. Strumpf suggests this was due to free nitric acid contained in the liquid, but a colleague of mine tells me he always suffers from colicky pains if he takes the pharmacopœial sp. æth. nitrosi.

[2] Nitro-glycerine in Angina Pectoris, p. 24.

Now, if this be the case, the failure of spiritus ætheris nitrosi as a diuretic so often noticed may be readily accounted for. Christison and many other writers speak of the frequency with which the drug disappoints our expectations when given as a diuretic; but since it is probable that it only acts if decrease of tension is necessary for diuresis, we cannot wonder that the expected result is often wanting. In cardiac dropsy, for example, the indications for spiritus ætheris nitrosi will rarely be present, and it is in cardiac dropsy that its failure to produce increased secretion has been specially complained of. Many years ago I noticed that spiritus ætheris nitrosi was especially useful as a diuretic in elderly people, with whom indeed it is the most popular domestic remedy for defective urinary secretion. It seems probable that its value in such cases may be connected with the increased tension which not unfrequently results from tissue changes. The short duration of the action of nitrous ether on the circulation, as compared with digitalis, will explain the want of permanence of its effects as a diuretic, even when it promotes excretion of water.

The diaphoretic influence of sweet spirit of nitre may be explained, like its diuretic influence, by its effects on the circulation. Under certain conditions the dilatation of the cutaneous vessels to which it gives rise is followed by perspiration, but since that dilatation is only one factor in the production of perspiration, the diaphoretic effects do not always follow the exhibition of the spirit. The connection between its influence on tension and its diaphoretic effect may enable us to judge of the probability of its usefulness as a diaphoretic in individual cases.

The tracings I have given explain the stimulant effect on the heart mentioned by W. G. Smith,[1] and its action as a diffusible stimulant which Stillé alludes to. It is evident that it may cause a tense small pulse to become fuller and stronger to the feel, and quicker. The heart's beat, too, may become perceptible to the patient under the influence of the ether, as it often does after the exhibition of amyl nitrite, nitro-glycerine, and the nitrites. The change which it effects in the circulation may also account for its utility in certain nervous symptoms in children to which Wood calls attention, and for its grateful stimulating effect in irritable conditions to which Smith refers.

With regard to the febrifuge action for which it is largely administered, there seems little doubt that this is also connected with the effect it has in dilating the cutaneous vessels and thus exposing a larger amount of blood to the air. It may, however, be connected with some direct influence of the drug on the tissues; for Wood has noticed that the fall of temperature which in animals follows on the exhibition of nitrite of amyl is accompanied by diminished excretion of CO_2.

I have not yet had the opportunity of trying spiritus ætheris nitrosi in angina pectoris. That it will be useful Dr. Hay's observations show, since he found its essential constituent, nitrite of ethyl, effectual in averting the attacks. It seems probable that it will not replace nitrite of soda or nitro-glycerine as a preventive of anginal attacks, yet it is worthy of trial. Wherever indeed nitrite of amyl or soda, or nitro-glycerine can be used beneficially, there we may find place for the use of nitrous ether. Asthma, some forms of headache, and certain disorders of menstruation have been benefited by nitro-glycerine. May it not be that in some of these ailments we shall find the exhibition of pure spirit of nitre also beneficial; that our failures with it have arisen partly from the administration of an impure spirit, partly from want of knowledge as to the physiological effects on which its therapeutic uses depend; and that the use of the genuine drug in proper cases may show us that the popular belief in the wide efficacy of sweet spirit of nitre is founded on fact?

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[1] Commentary on the Pharmacopœia, p. 646.

NITRITE OF ETHYL.

1888.

The extensive literature which has appeared during the past ten years bearing on the therapeutic uses of the nitrites, points to increasing appreciation of their value, but nitrite of ethyl, which has been longest before the medical profession, has so far received but scant attention. The varying character of the official preparation sold as spiritus ætheris nitrosi, has doubtless been the chief cause for this neglect.

The older processes recommended for the preparation of this spirit, did not lead to a product of uniform composition, and the methods devised for determining the amount of nitrite of ethyl in any sample have been either very unreliable or so intricate that they could only be employed by those constantly engaged in chemical manipulation.

Of late years, however, much attention has been devoted by pharmacists to spirit of nitrous ether. A better method for its production has been introducd, and its assay has been rendered easy by the methods for its analysis invented by Eykman of Tokio, Allen of Sheffield, and others. But it has been found that however well made spirit of nitrous ether may be, it tends rapidly to lose its ethyl nitrite if dispensed in the ordinary way, and pharmaceutical chemists have sought to devise preparations better adapted for retaining a definite strength of the ethyl salt than the ordinary spirit of nitre.

About two years ago Williams showed that glycerine tends to prevent the loss of nitrite of ethyl from its solution in alcohol; and last April Dunstan and Dymond proposed a new method of making ethyl nitrite, and suggested a preparation which might be employed medicinally. It consists of a dilute solution of nitrite of ethyl in absolute alcohol, or in absolute alcohol containing five per cent. of glycerine, and analyses were given showing that thus dissolved the ethyl nitrite solution may be long kept without important change.

I have recently made trial of two solutions of this kind which Professor Dunstan has been good enough to forward me—one contained a little under two per cent., and the other about three per cent. of nitrite of ethyl, and from the results obtained I am satisfied that the introduction of such a solution into general use would prove very advantageous.

For nitrite of ethyl has pharmacological properties which render it in fitting cases of the highest therapeutic value. Like other nitrites, it causes dilatation of the vessels, and markedly decreases arterial tension. It not only relaxes the muscles of the arterioles, but also, as Professor Fraser has shown, of those of the smaller bronchial tubes; thus dilating bronchial tubes unduly narrowed by spasmodic contraction of their muscles.

An important point to bear in mind with regard to the action of nitrite of ethyl is the fact that its influence is not by any means as rapid as that of nitrite of amyl when administered by inhalation, and several minutes elapse before its action on the vessels is distinctly perceptible. Marked tension fall, indeed, is usually only observed from five to fifteen minutes after the administration of an ordinary dose, though the drug doubtless exerts some influence within a much shorter period, and its effect on the bronchial muscles sometimes becomes perceptible in less than a minute. Its physiological influence is often distinct for half an hour to an hour, and may at times be traced for a much longer period. In this respect ethyl nitrite resembles nitro-glycerine, and differs from nitrite of amyl, the action of which, at least when inhaled, rarely lasts more than two or three minutes.

The dose required to produce the physiological effects is very small. Half a drachm of a 3 per cent. solution will usually produce dilatation of the vessels, which may be distinctly shown by the lowered tension of the pulse. A much smaller amount will sometimes suffice for this effect, and I have not met with anyone whose circulation was not affected by a drachm.

Turning now to the therapeutic uses of the solution of nitrite of ethyl, I may say that as a diuretic and diaphoretic it is, like other nitrites, inconstant in action. No proof has yet been offered that these bodies directly stimulate the glandular secreting structures. When they produce any effect it is by their power of dilating the vessels. In the kidney the blood-flow through the glomerular vessels is thus rendered more rapid, hence the watery excretion is at times augmented. The skin secretion is probably under certain conditions increased by the additional blood supply to the tissues amongst which the sudoriparous glands lie. The effect of the drug will doubtless vary with the condition of the circulation at the time of administration. It is certainly not a reliable diuretic, for doses of half a drachm to one drachm of 3 per cent. solution often fail to affect the urine secretion. On the other hand, I have seen an increase both in renal and cardiac disease after its use, and it is worthy of trial, especially in the elderly, or where the tension is high. In the healthy the diaphoretic action is not often observed, but under some conditions it produces an increased action of the skin, and it will probably be found of use in catarrhal conditions. I can certainly bear personal testimony to the diaphoretic influence produced on me by drachm doses of a 3 per cent. solution during an attack of febrile catarrh.

In the treatment of ailments connected with high tension, ethyl nitrite solution is of great value. I have found it prevent the advent of anginal attacks, just as nitro-glycerine does, but like nitro-glycerine, it is not of service in removing at once anginal pain. For this purpose its action is too slow. In cases of dyspnœa where with high tension the heart's power is beginning to fail, nitrite of ethyl often acts like a charm, and this is especially the case if, as not unfrequently happens, bronchial spasm complicates the cardiac condition. Not only is breathing relieved, but the pulse becomes fuller and altogether of better character. Like nitro-glycerine, it sometimes seems to act as a cardiac stimulant, but this effect may only be due to the relief afforded to the heart by the dilatation of the vessels. Wherever with fair tension the heart's power is weak and dyspnœa is present, the administration of 30 to 90 minims of a 3 per cent. solution of nitrite of ethyl is worthy of a trial. But it is perhaps in asthmatic and bronchitic affections that the nitrite will be found of the most marked benefit. Professor Fraser, in a recent paper (*Trans. Ed. Med. Chir. Soc.*, vol. VI.), has given cases illustrating the use of the various nitrites in these ailments, and my experience with nitrite of ethyl entirely accords with the results he obtained.

In genuine asthma I have so far had no opportunity of trying it, but in that form which so often complicates bronchitis I have usually found 50 to 90 minims of a 3 per cent. solution of nitrite of ethyl give more or less relief. The direct effect of the drug lasts from 30 to 90 minutes, or longer, and even when this must have ceased the spasmodic trouble does not always return. The utility of nitrite of ethyl may be illustrated by the following case:—

F. R., aged 30, who has before suffered from bronchitis, was exposed to cold on the 18th of October, and on the same evening felt feverish, with some "tightness of the chest and wheezing," which prevented much sleep. She took an expectorant, and during the following day seemed somewhat better, but at night I found her with a temperature of 100°, and breathing with much difficulty. Sibilant rhonchi could be heard all over the chest. In previous attacks all forms of expectorants, and even emetics had failed to relieve quickly, and inhalations had not proved of much service. I gave her 60 minims of the 3 per cent. solution of nitrous ethyl. In a few minutes she was easier, and next morning she informed me that within twenty minutes she was quite relieved and began to perspire. After this she soon slept, and during the night had no further trouble. On two subsequent nights slighter attacks of the same kind came on, but were at once removed by the solution. Other remedies will undoubtedly sometimes produce a similar effect, but so far I have met with none so constantly effectual.

In capillary bronchitis I have not tried the drug, nor have I used it where moist rhonchi predominate, but wherever there is reason to believe that undue contraction of the involuntary fibre surrounding the bronchi adds to the dyspnœa, I believe nitrite of ethyl may be tried with a good hope of at least temporary relief. It is quite possible that in affections due to spasm of the involuntary fibres of other organs, as for example, the stomach, it might be found beneficial.

The solution of ethyl nitrite in alcohol possesses two advantages over spiritus ætheris nitrosi; it is more stable and less disagreeable. Mr. Elborne kindly estimated, from time to time, the amount of nitrite present in the preparations used by me, and the loss of nitrite was certainly very slight, though no special care was taken to prevent the escape of the nitrite. A four ounce bottle, of a 2·7 per cent. solution, lost 0·4 of this per centage during its use in six weeks, and from a weaker, but better prepared solution, the loss during a longer time was much less. The advantage which the solution possesses over ordinary spirit of nitre, as regards taste, depends on the absence of aldehyde and other products of the complex chemical changes which take place during the formation of the spirit of nitrous ether.

The question, however, arises: Does the presence of these products give any therapeutic power to the spirit of nitrous ether which is not possessed by a simple solution of nitrite of ethyl in alcohol? I am satisfied it does not. There is no reason for believing that any of them can so contribute. The physiological action of aldehyde is not well known, but it seems to possess no properties calculated to increase the efficacy of the nitrite, and we have no reason for believing the other substances, traces of which have been found in spirit of nitre, in any way influence its therapeutic action. Then, again, every effect which spiritus ætheris nitrosi produces can be explained by the physiological effects of ethyl nitrite apart from any of these agents, and the therapeutic action of a simple solution of nitrite of ethyl in alcohol, and of the ordinary spiritus ætheris nitrosi are practically identical. Both are inconstant diuretics and diaphoretics. The spirit, indeed, is so inconstant that it is rarely relied on alone, but almost always, by medical men at least, it is given in conjunction with other agents having a like action.

In a former paper,[1] I have shown the marked effect of spirit of nitrous ether, when properly prepared, on the circulation, and it would ere this have played a more definite *rôle* in the therapeutics of the circulatory organs, had its composition been more constant. Probably, indeed, it is to the effect which the nitrite of ethyl contained in the spirit as ordinarily supplied has on the circulation that the popularity of "sweet nitre," both with the public and the profession, is largely due, for a very small quantity of the nitrite may somewhat lighten the load a heart has to bear, and cause a feeling of comfort without producing any other perceptible effect.

The influence now claimed for nitrite of ethyl over the respiratory organs is greater than that which has generally been accorded to the Pharmacopœial preparation, yet it must be remembered that spirit of nitre has been for ages a favourite remedy in bronchial catarrh, though the cause of its utility was not known. And doubtless the good effects produced in bronchitis would have been more noticed, had the preparation employed contained a due amount of nitrite. A preparation in which there is less than 2 per cent. of the ethyl salt is not likely to influence the bronchial muscles unless employed in larger doses than are usually administered, but the greater part of the spirit of nitre given has always contained much less than this. In our present hospital compound for example, I found only 0·3 per cent.

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[1] P. 29, also "Practitioner," Oct., 1883.

It is, indeed, perhaps well that the nitrous ether commonly sold contains only a small quantity of its active ingredient, for large doses of the nitrite of ethyl may so influence the circulation as to cause faintness either by too rapidly reducing the resistance against which the heart has to contract, or by acting directly on this organ. This effect I have seen produced by 100 minims of good spirit of nitrous ether, and the same result occurred to myself after taking 25 minims of a 25 per cent. solution. It would perhaps therefore lead to trouble sometimes if spirit of nitre, as supplied to the public, did always contain its due amount of nitrite.

For the due therapeutic use of nitrite of ethyl it is most important that medical men should know the strength of the solution they give, for it is often necessary to accommodate the dose to the peculiarities of the patient. Some are very susceptible to the action of the drug. I have known less than a drachm of a 2 per cent. solution produce the throbbing in the head characteristic of the nitrites, whilst others will take three times the dose without suffering from any subjective discomforts. The effect of the drug in disease will largely depend on the dose given. Hence, if it is to be used effectively, we must be supplied with a solution of definite strength, which can be readily analysed and readily kept up to a definite standard. Such a solution as that suggested by Dunstan and Dymond seems to fulfil the conditions required, and might be introduced into the Pharamcopœia as "Solution of Nitrous Ether," or "Solution of Ethyl Nitrite." The spirit might then be relegated to the use of the public. As ordinarily supplied it could do no harm, and it might sometimes do good. One point, however, will have to be borne in mind. Solution of nitrite of ethyl decomposes quickly when in contact with water. To obtain reliable results from it, therefore, it should not be dispensed mixed with water, but separately; the requisite dose being measured out and added to water immediately before administration.

COMPARATIVE EFFECTS OF SPIRITUS ÆTHERIS NITROSI AND SOLUTION OF NITRITE OF ETHYL.

1888.

In the *Practitioner* for October, 1883, I pointed out that spiritus ætheris nitrosi answering to the tests in the British Pharmacopœia has a distinct influence on the circulation, and suggested that the therapeutic value of the drug was chiefly due to this effect, which is manifestly dependent on the nitrite of ethyl contained in the spirit. The question of the practical identity of the action of spirit of nitrous ether and solution of nitrite of ethyl has not yet been definitively settled, and as it is one which in recent years has specially interested pharmacists, I am glad to take this opportunity of setting forth the conclusions I have arrived at.

Pharmacological considerations certainly render such identity probable. Of the various substances present in the spirit in addition to nitrite of ethyl and alcohol, aldehyde is perhaps the most abundant. But aldehyde has no properties which lead us to suspect that it has any influence on the physiological action of the spirit. It does not appear to interfere with the circulation when given in quantities much larger than are contained in medicinal doses of spiritus ætheris nitrosi, for I have watched the effects of 20 minims on myself and others, and have failed to find the slightest change produced on the pulse. Large and even small doses sometimes irritate the stomach, and in considerable quantities it causes in animals a comatose condition and likewise arrests respiration, but there are no reasons for believing that the amount contained in spirit of nitrous ether ever gives rise to an appreciable physiological effect. Paraldehyde, too, which may be contained in spiritus ætheris nitrosi, though reducing pulse tension in doses of 50 minims and upwards, and acting as a sedative in smaller doses, is not present in sufficient quantity to materially influence the action of the spirit, nor is there reason for believing that any one of the other oxidation products can by itself produce a definite effect when taken in minute quantities.

But though no single constituent of spiritus ætheris nitrosi, apart from the alcohol and the ether, either adds to or alters its physiological or therapeutic action, yet these constituents combined might have a distinct effect. To determine whether this is so or not I have made some experiments as to the comparative influence of spiritus ætheris nitrosi, answering to the tests of the British Pharmacopœia, and a 2·25 to 2·7 per cent. solution of nitrite of ethyl in absolute alcohol containing 5 per cent. of glycerine, kindly supplied to me by Professor Dunstan, Director of the Research Laboratory of this [1] Society. Both dilate the vessels and decrease tension, and both remove undue contraction of the muscular coats of the bronchial tubes, but neither the spirit nor the solution have any powerful and constant influence on the skin or kidneys. I have given them repeatedly in doses of a drachm to two drachms to healthy people without noting any increased action on the skin, but if the subject of experiment be kept in bed and somewhat more warmly covered than usual, one, or more frequently two doses of either commonly produce perspiration. I have not, however, been able to discover any difference between the activity of the spirit and that of the solution, nor do they differ, as far as I can ascertain, in their action on the kidneys. At times, after both, a slight increase in the urine flow seems to occur, but more frequently no changes are observed.

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[1] Pharmaceutical Society.

It is more difficult to compare the therapeutic uses than the physiological effects of two preparations. Spirit of nitre has long been a popular remedy for causing the increase of the urine flow and perspiration, but chiefly in those ailments where such increases occur naturally at a certain stage of the ailment, as, for example, in feverish colds. I believe it certainly does hasten a critical perspiration by increasing the blood flow through the skin, so, too, does the solution of ethyl nitrite, but I can find no ground for believing that one is more effectual than the other. As diuretics, both spirit and solution have seemed to me even less reliable than as diaphoretics, hence comparison is difficult, but so far I have been unable to detect any difference in the power of the two preparations.

In ailments connected with narrowing of the arterioles, and in difficulty of breathing due to contraction of the muscles of the small bronchial tubes, the spirit and the solution are of great, and I think of equal, value; they tend to prevent the advent of attacks of angina pectoris, and by dilating the arterioles, they relieve an overloaded heart. The popularity of spirit of nitre as a medicine depends, it seems to me, largely on this latter effect; even a very small dose of nitrite of ethyl will thus remove discomfort.

In difficulty of breathing, due to contraction of the smaller bronchial tubes, the administration of a drachm to a drachm and a half of spirit of proper strength often gives great relief; so, too, does solution containing an equivalent amount of nitrite of ethyl; but a spirit poor in nitrite will often fail to do any good. I found our hospital preparation ineffectual in such cases, and then ascertained that the percentage of ethyl nitrite, though doubtless sufficient at first, had fallen to ·3 per cent., the spirit having been in stock six months.

I need not allude in detail to the less important properties of the spirit and solution of nitrous ether. I have found no evidence that the two preparations differ at all in their therapeutic effects, provided the doses given contain an equivalent amount of nitrite of ethyl, and I am satisfied that a solution such as I have used will answer every medical purpose served by spiritus ætheris nitrosi.

The variations in the strength of the spirit used in time past has prevented due appreciation of one of its most useful properties, that of relieving certain forms of difficulty of breathing, and it is manifest that in order to get from nitrite of ethyl the results desired, it is essential that medical men should be supplied with a solution which can be always relied on to contain a known quantity. For another reason, too, it is most desirable that they should be able to know exactly the amount of the ethyl compound contained in the preparation they give. Experience has shown that susceptibility to the nitrites differs greatly; symptoms such as throbbing headache and other troubles are in some produced even by small doses, whilst others can take comparatively large quantities without noticing any subjective symptoms. In giving nitrite of ethyl, the possibility of such variations has to be taken into account, and the dose has to be graduated to the patient as well as to his ailment, for a dose which proves curative in one case, will in another entirely fail to give relief, owing to difference in susceptibility. Such graduation is of course impossible, unless we are supplied with a preparation of fairly constant strength.

Fortunately nitrites, even when given in excessive amounts, hardly ever give rise to serious troubles, but the faintness and uncomfortable sensations I once experienced after a small quantity of a 25 per cent. solution would make me cautious about giving a dose which might be excessive in relation to the patient. I have seen, too, 90 minims of a spirit of full strength cause slight faintness, and it seems to me a solution of definite strength is necessary for the sake of safety when full doses are given.

The solution in alcohol and glycerine suggested by Professor Dunstan and Mr. Dymond, last April, seems very well adapted for the administration of nitrite of ethyl, and from occasional examinations made of the strength of specimens in use, I can confirm Professor Dunstan's statement as to its stability. The large amount of alcohol which is required to administer such a dose as two minims of the nitrite seems to me its only drawback; but the combination of the nitrite and alcohol is in itself, I think, useful, and if alcohol be not desirable, a nitrite soluble in water may be given in place of the ethyl compound, since all nitrites have a similar influence.

I believe, then, that the introduction of a fairly stable solution of ethyl nitrite is now called for, and that the time-honoured spiritus ætheris nitrosi should disappear from the list of official remedies, since on account of its ready decomposition it is not adapted for administering the nitrite in definite doses. Should, however, there be any who find, or think they find, an advantage in the spirit, and both be included in the Pharmacopœia, it seems to me the present test of purity of the spirit would not be needed. For then the ethyl nitrite could hardly be considered the cause of this advantage, and this being so it would not be necessary to ask that it should contain a definite percentage of the nitrite. Certainly "sweet nitre" should not be required to contain as much as 2 to 3 per cent. of ethyl nitrite. I cannot help thinking that had it been easy to maintain so high a standard we should have heard of more evils arising from the popular use of this drug than we have done.

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ON THE
DURATION OF THE ACTION OF MEDICINES,
WITH ESPECIAL REFERENCE TO
THE NITRITES AND NITRO-GLYCERINE.

1885.

In the treatment of disease by medicines, we have to determine the frequency with which a drug must be given, as well as the quantity in which it should be administered. Experience doubtless aids us in deciding as to the periods which should intervene between successive doses of medicines; but I believe most practitioners will agree with me that, in a large majority of cases, the frequency of repetition is, to a great extent, a matter of routine. The custom of administering medicines at regular intervals of three or four hours—a little oftener when the case is severe, at longer intervals as it becomes milder—has come down to us from a time when the knowledge, both of disease and of drugs, was less advanced than it is now. Disease was formerly looked upon as an enemy to be attacked and routed by medicine; if the enemy were in strong force, it was considered desirable that a strong fire should be maintained at short intervals. If he showed signs of retiring, the fire was slackened in its severity, in its frequency, or in both. The exact manner in which medicines effected the cure of disease was either not considered at all, or was the subject of vague speculation. But, at the present time, one of the leading objects of the therapeutist is to alter the functions of certain tissues or organs, temporarily or permanently. Sometimes we aim at restoring the normal functions of parts, sometimes we desire to modify functions for a time, and thus neutralise evils arising from a disordered condition of other parts on which we cannot act. But whether our purpose be to restore or modify, we know it can rarely be attained except by acting on the tissues or organs we wish to influence, with a certain degree of continuity; and we should endeavour, therefore, to repeat our medicines in such doses, and at such intervals, that the continuity of action we desire may be attained.

If this be so, it is manifest that our knowledge of the length of time during which a medicine can be counted on to act on any organ, ought to play an important part in our decision as to its repetition. Unfortunately, our information as to the duration of action of some drugs is very limited, and the causes which lead to variations in duration are only obscurely known to us. I believe, however, that further investigations may furnish us with additional knowledge on these points which will render our therapeutic proceedings more exact, and in this way add to our power of combating disease.

Now, first of all, the question may be raised, does our present knowledge support the view that medicines act during definite periods; that is, can we rely on a given dose of a drug influencing the organ upon which it acts for the same space of time in different individuals, or on the same individual at different times?

It must be confessed that some of our experiences seem at first sight to give a negative answer. We know that if a number of persons take a poison together, the effects may commence and terminate at different times. A dose of arsenic may cause violent symptoms in ten minutes, but ten hours may elapse before evidences of poisoning appear, and the period at which death occurs may vary in a corresponding manner.

Differences with regard to the effects of poisons can be, to a great extent, explained by differences in the rapidity with which the absorption commences. As long as a poison remains quite unabsorbed in the stomach, it cannot, of course, exert its usual effects on other organs; and toxic substances seem at times to influence the stomach in such a manner that absorption is materially delayed.

Drugs in medicinal doses are less liable to raise up barriers to their own absorption, but a very slight alteration in the condition of the stomach may delay the solution of the materials which, ordinarily, are quickly digested; and there can be little doubt that drugs, even in medicinal doses, may at times remain long unchanged after they are swallowed. Sometimes they are then rejected; most of us have seen cases in which a dose of medicine has been returned after a sojourn of an hour or two in the stomach. But sometimes absorption at length takes place, and then the ordinary physiological effects appear, though at a late period. Deferred absorption, probably, accounts for most of those instances in which the action of medicines is unduly delayed.

When the absorption of a drug commences without any unusual delay, the duration of its action will depend chiefly on the time required for the completion of this process, and on the rapidity with which excretion of the drug takes place. It will likewise be influenced by the susceptibility of the part affected, for we may well suppose that the more powerfully an organ is acted upon, the longer will the disturbance in its functions continue, even though the cause of the disturbance has passed away. Now, susceptibility of an organ to the influence of a drug may vary considerably in different people, and likewise in the same individual, according to state of health and other circumstances.

Manifestly, the conditions which regulate the duration of the actions of medicines are exceedingly complex. I shall try, however, to show that, apart from exceptional circumstances connected with absorption, many medicines do act for tolerably definite periods; and, in some cases, it may be possible to determine the average time of action of individual doses with sufficient exactness to serve as a guide to repetition.

In the first place it may be pointed out that experience has already made us aware of relative uniformity in the period of activity of many drugs. Ammonia acts quickly on the heart, and its effects soon pass away; the tonic effects of digitalis are slow to appear, but they last a long time. Of our diuretics, purgatives, and emetics, some act for a shorter, some for a longer, period. The diuretic effects of caffeine, for example, soon cease when we stop the administration of this drug, whilst the increased flow of urine which is produced by digitalis usually goes on for a long time, sometimes for several days, after the medicine has been discontinued. The difference in the period during which these two drugs act, may of course depend on the fact that they exert their influence on different tissues. Caffeine, it has been suggested, stimulates the tubular epithelium, whilst digitalis causes diuresis through its effects on the vascular system. But the relative difference in the duration of action must certainly be dependent on the fact that each influences the tissues it affects for a more or less definite period. We find, too, that when drugs act in a similar manner on the same tissues, the relative periods of their activity may vary distinctly.

The symptoms of intoxication produced by alcohol can be reproduced by ether, and there can be little doubt that, in inducing their usual results, these two drugs affect the same tissues and functions. But each stage of intoxication is shorter, when caused by ether, than when it is due to alcohol, and as the relative difference of activity is always to be observed, it is manifest that the duration of the influence of these two drugs, on the parts of the body they affect, must be, within certain limits, definite. What these limits are, has not yet been ascertained; but in the case of a class of drugs which yield symptoms capable of graphic representation, the limits of duration may be, to a certain extent, demonstrated.

The marked phenomena produced by the inhalation of nitrite of amyl, and the resemblance between them and those which follow the administration of other nitrites and nitro-glycerine, have been made known to us by the investigations of Drs. Brunton and Cash, Dr. Murrell, Dr. Hay, and others; but all who have made observations on the comparative effects of these substances have noted the great difference there is between the duration of the influence of the amyl compound and that of the other nitrites and nitro-glycerine. Dr. Murrell has pointed out that, while the influence of amyl nitrite is very transitory—a tracing taken a minute and a half after the inhalation of the drug appearing normal — the full action of nitro-glycerine is not observed in the sphygmographic tracing till six or seven minutes after the dose has been swallowed, and the tracing does not assume its normal condition for half an hour. Dr. Hay has further drawn attention to the fact, that nitrite of sodium checks anginal pains for a longer time than nitro-glycerine, from which it follows that the influence of the alkaline nitrite on arterial tension persists longer than that of the glycerine compound.

But it has been noticed, too, that the phenomena produced by the nitrites and nitro-glycerine vary not a little in different individuals. Some people, for example, are powerfully affected by half a drop of a one per cent. solution of nitro-glycerine, but many can take five drops, and some even a larger quantity, without feeling any sense of discomfort.

In endeavouring, therefore, to determine the period during which nitro-glycerine and the nitrites depress tension, I have administered these drugs in various doses to individuals differing considerably in susceptibility to their effects; and, though the number of experiments is not sufficient to fix absolutely the limits of the duration of their action, I think that the results show that an approximately correct estimate of these limits may be obtained.

I may point out that I have devoted my attention especially to the effects of the drugs on arterial tension. It would be quite possible to determine the time during which they alter the frequency of the pulse, or produce subjective phenomena, and this time might or might not accord with their influence on arterial pressure.

It seemed to me, however, better, in the first place, to limit my attention to one point only. In all cases in which I have made observations, to determine the duration of the effects of drugs on circulation, tracings were first taken, frequently for three or four days, to determine the variations of the pulse apart from medicinal influence. In some, these variations are considerable, and such I have rejected for experimental purposes, choosing those only from whom I found that fairly uniform tracings could be obtained. The subjects of my experiments were all free from cardiac disease. The observations were made, as far as possible, under similar conditions as regards time of day, food, etc.

The influence of amyl nitrite on the pulse commences immediately after its inhalation. The arterial tension is reduced to its lowest point in thirty to sixty seconds; the blood-pressure then rises again, and usually attains its ordinary height in a minute and a half, as stated by Dr. Murrell. But at times the normal tension is not quite reached for two to four minutes; and, not unfrequently, a fall of tension follows in a few minutes after the apparent recovery, so that really the return to normal is not accomplished for eight or ten minutes. A further slight fall may follow on this second return, the effects of the nitrite on the pulse being traceable by the sphygmograph for twenty minutes to half an hour. Alternations of this kind occur during the action of all the nitrites, and I shall allude to them as oscillations. Occasionally, the blood-pressure does not rise quite to its proper height in the first few minutes, a distinct fall in tension taking place after the pulse has only partially regained its normal character; and the average blood-pressure, in a few cases, is not reached for an hour.

In only one instance (Figs. 19—25) have I been able to trace the effect of the nitrite of amyl for more than an hour. Here, a minute and a quarter after the contents of one of Martindale's capsules were inhaled, the pulse had partially regained its ordinary tension. Four minutes afterwards, the pressure was somewhat higher, but still had not quite reached its normal condition. Six minutes after this, a slight fall in tension was noted, and soon after, again a very slight rise. Then there was a fall. After this it gradually rose, but with slight oscillations; and 1 hour and 15 minutes after inhaling the nitrite, it regained permanently its ordinary condition. I should have deemed it almost impossible for the amyl compound to act for so long a time, had I not known that the subjective effects of the drug often continue long after its pronounced effects on the circulation have disappeared.

The duration, then, of the effects of nitrite of amyl varies considerably; its very marked tension-reducing influence never lasts more than one and a half to two minutes, but a slight depression of blood-pressure is commonly present for a longer period, and not only does the duration of the influence of the amyl nitrite differ in different people, but it is also variable in the same individual at different times. Of two successive doses, the influence of one may be traced for half an hour, whilst the effects of the other may disappear in the course of a few minutes; but this remark only refers to the slighter effects, very distinct lowering is of the same duration in all.

Nitrite of ethyl depresses tension for a much longer time than amyl nitrite, and in quite a different manner.

A dose of 25 minims of a 25 per cent. solution, in alcohol, causes, in those susceptible to the influence of the nitrites, a slight fall in tension within a few minutes; but, as a rule, the greatest effect is not noticed until from six to fifteen minutes have elapsed. For twenty or thirty minutes longer, the tension continues low. Then a return towards the normal takes place, usually with oscillations. I have traced the effect of this nitrite for two hours. Where the dose is small, or in those not very susceptible to the action of the nitrites, hardly any fall is seen during the first half-hour, and the normal tension is regained in about an hour and a half. Figs. 26—32 illustrate the influence of 25 minims of a 25 per cent. solution on a subject (L.) very susceptible to the influence of nitrites. Figs. 33—36 show the effects of the same dose in a man (S.) with hemiplegia and high tension. In L., the administration of this nitrite caused, in half an hour, such faintness, as to compel him to assume the recumbent position; slight traces of the influence of the drug on the pulse could be detected two hours after administration.

I have not made a sufficient number of observations with the alcoholic solution of ethyl-nitrite to satisfy myself as to the exact limits of the time during which it acts. But, from some experiments made with spirit of nitrous ether, answering to the British Pharmacopœia test, I believe that seven or eight minims of pure ethyl-nitrite will usually keep the tension distinctly depressed for at least forty-five minutes, in some people for rather more than an hour; and that the circulation is often influenced during the whole of the second hour after administration. The depression of the tension, though more prolonged, is not so great as that produced by nitrite of amyl.

Nitro-glycerine acts more quickly and more powerfully than nitrite of ethyl; its effects, too, are more prolonged. A single drop of a 1 per cent. solution usually causes a fall in the pulse-tension in one and a half to two minutes, and in three or four minutes the fall is well marked. The blood-pressure continues low for about ten minutes, sometimes a little longer; then it gradually rises, and in half an hour may be almost normal. But, after this, oscillations commonly take place, and the normal standard is not usually perfectly attained for an hour to an hour and a half after the drug has been given. (Figs. 37—42).

The effects of two or three minims are often well seen for nearly an hour; after this they are not well marked, but are perceptible for some time. In about an hour and a half, the tracing has returned to the form it had before the drug was given. But even after this, slight oscillations may appear, as in the case of nitrite of amyl. If a large dose be given, the effects are often distinct for an hour and a half, and traceable for two hours and a half (Figs. 43—56).

But nitro-glycerine acts on some individuals more powerfully, and for a longer time. Figs. 57—65 show the effect of a single drop of a 1 per cent. solution on the pulse of W. H., one of the most susceptible of all the subjects on whom I have experimented. It will be seen that the tension was very distinctly lowered for one hour and a half; then it gradually rose; but in three hours and a half it had not quite regained its normal height. I never ventured to give W. H. a larger dose; but to another susceptible man (V. C.) I gave three minims and a half; and the results are set forth in Figs. 50—56. Here for an hour the tension remained extremely low, and in an hour and a half it had by no means regained its proper height. Even the return, in two hours and ten minutes, was not permanent, a slight fall being once or twice observed in the ensuing forty minutes.

It is manifest that we cannot look on half an hour as the limit of the tension-reducing effect of even small doses of nitro-glycerine; and, from a large series of tracings I have taken, it seems to me that, as a rule, a dose of one to two minims of the 1 per cent. solution exercises its most powerful effect in the first half-hour, but that it usually affects the pulse for an hour longer, that a larger dose, five minims (Figs. 66—73), does not depress the tension markedly for more than three-fourths of an hour, and its effects are apparent for two to two and a half hours; but that, in those very susceptible to the influence of nitrites, marked lowering of pulse-tension is kept up for an hour or more, whilst some influence can be detected for three hours, and sometimes a little longer.

The tracings I have taken after the administration of the nitrites of sodium and potassium confirm the view already expressed by Dr. Hay, that the duration of the effects of the alkaline nitrites is more prolonged than those produced by nitro-glycerine. The influence of the alkaline nitrites is not exerted so quickly as that of nitro-glycerine. In most cases, ten minutes elapse before the tension falls markedly; but a slight change is seen within the first five minutes. Size of dose exercises only a slight influence on the time of commencement; but those who are very susceptible to the action of nitrites are affected in six minutes as strongly as ordinary people are in ten. After the first ten minutes, the pressure falls rapidly, and it remains usually very low from the end of the first half hour until about two hours have elapsed from the time that the drug was administered. But slight oscillations in the pressure are always present during this period. Oscillations, too, are noted during the rise of the pulse to the normal pressure, which is reached in from four to five hours.

From a number of observations, I estimate that, whilst the average duration of five grains of an alkaline nitrite in ordinary individuals is about four and a half hours, the effect of three grains does not last so long by half an hour. Figs. 74—81 show the influence of five grains in a moderately susceptible man. Though the influence of nitrites on the degree of tension is more marked in those whom I have designated susceptible, I do not find that in such people the duration of the effect is materially greater.

Figs. 81—89 show the tracings taken after the administration of four grains of nitrite of potassium to a man very susceptible to the action of nitrites, but the dose required to produce fall in tension in the susceptible is very small. In Figs. 90—96 is seen the influence produced in a very susceptible man by half a grain of nitrite of sodium.

The duration of the action of a drug is doubtless in part dependent on the rapidity with which it is absorbed from the stomach, and it seemed to me possible that a more prolonged effect on tension might be obtained by a substance less soluble than the alkaline nitrites. I, therefore, tried the effect of cobalt yellow, a double nitrite of cobalt and potassium. I found it somewhat irregular in its action; in some individuals, three or four grains produced very little fall in pressure, but in others, as seen in Figs. 97—103, the influence was considerable, four grains lowering the tension greatly for three hours and ten minutes. Seven grains, in one case (Figs. 104—110) affected the tension for six hours; but, generally, the duration of its action was not more considerable than that of the nitrites; the effects appear, however, later, twenty to thirty minutes usually elapsing before the tension is much lowered.

In estimating the duration of the effects of tensor-depressants, the oscillations which occur, both during the rise and fall of blood-pressure, cause considerable trouble. It is difficult to fix the exact time at which the tension becomes permanently normal, as well as the time at which it reaches its lowest point. The influence of the nitrites, indeed, seems, to a certain extent, wave-like. When the tension is falling rapidly, oscillations can hardly be detected; but, both when it is low and when it is rising, they are often very conspicuous.[1]

I have only looked on the return to normal as complete when the tracing has indicated the same tension as before the drug was given on several consecutive trials. I do not pretend, as I have said, that the observations I have made determine accurately the limits of the tension-depressing effects of the compounds with which I have experimented, but they certainly seem to show that these substances act for a fairly definite time. Nitrite of amyl acts powerfully almost at once, and for two minutes, but its influence on the pulse may often be traced for ten to twenty minutes, sometimes longer. The effects of nitrite of ethyl are best seen five to twenty minutes after its administration, but remain very visible for an hour, and are perceptible for one and a half to two hours. Nitro-glycerine powerfully affects the circulation in two minutes; its influence is most marked for thirty to forty-five minutes, and may be detected for two and a half to three hours. The alkaline nitrites produce but little influence on pressure for from six to ten minutes, but then depress it strongly, for two and a half hours, and act altogether for between four and five hours. Cobalt yellow begins to act markedly in from twenty to thirty minutes; its tension-depressing effects are often very pronounced for more than three hours, and sometimes visible for six hours.

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[1] Van der Heide (*Arch. für exp. Path. und Pharm.*, xix., p. 139) has noted in animals similar oscillations during the return of the blood-pressure to the normal, after it has been affected by digitalis.

The times I have named are, of course, averages. As I have pointed out, the period during which drugs act on individuals is influenced by the natural susceptibilities of the organs affected, by the dose, and by the condition of the absorptive and excretive powers. It therefore follows that the duration of action must differ within certain limits, not only in different individuals, but also in the same individual at different times.

The state of the organs connected with absorption and excretion is hardly ever the same for any length of time, and so it comes to pass that even consecutive doses in the same individual often vary, to some extent, in the period of their action. If, however, we can arrive at some idea of the average time during which we can count on single doses of our medicines acting, and the limits of variation in duration under different conditions, we shall have gained much.

Susceptibility can usually be determined by experiment, and sometimes judged of in other ways. In the case of the nitrites, for example, a single administration, if carefully watched, may enable us to decide as to whether the subject is easily affected or the reverse; but we may form an opinion on this point from the general characters of the circulatory system. The anæmic, and those of weak circulation, are usually powerfully affected by tension-depressants; those who have a high arterial tension, are not so readily influenced. In judging of the effects of diseases of organs on duration, we can only be guided by accumulated knowledge of the influence which disease has on absorption and excretion, and on the susceptibility of the organs which the drug acts upon. The dose required to produce an average effect as regards duration, will not be difficult to decide when the other factors which influence duration are known.

The effect of tolerance and cumulative action in altering the duration of successive doses, still requires consideration. I have several times carefully watched the effects of three or four doses of the various nitrites given in succession, with the view of ascertaining whether the length of time of the tension-reducing effect of the individual doses was thereby influenced, but I have found no indications that it was so; and in two Cases, who have taken nitrites frequently during several weeks, I have not found the duration of their tension-depressing effects materially altered; but further investigations are needed to decide the influence of tolerance and cumulative action on these as on other drugs.

Notwithstanding the difficulties which beset the utilisation of a knowledge of the duration of the action of the separate doses of drugs, it seems to me that the advantages of this knowledge are sufficient to warrant a further investigation into this hitherto neglected subject. The benefit which may be derived from such knowledge is well seen in the case of the nitrites. We have now the power of depressing, for any time we like, arterial tension. We may influence it for a few seconds, we may keep it low for hours; and when we consider the advantages which accrue in certain conditions from lowered tension, it is manifest that we have acquired almost a new therapeutic power. I have no doubt that, before long, we shall be able, in like manner, to raise arterial tension for definite periods of time.

Van der Heide has already made some experiments which bear on the duration of the influence of digitalis, in single and repeated doses, on animals. As might be expected from the knowledge we already possess, the length of time during which this drug acts was found to be very considerable, two or three days sometimes elapsing after the administration of the drug before the blood-pressure fell to its normal level. But the researches of Schmiedeberg and others have shown that there are numerous substances acting like digitalis, but differing considerably in their solubility in water. It seems to me probable that we may find amongst these some which act for a short time, some for a long time; and that, as in the case of the tensor-depressants, we may be able to arrange them in series, according to their duration. A further addition would then be made to our curative powers. I have already made a few preliminary experiments with helleborein; and, though I cannot at present be quite certain of my results, its tension-raising effects seem to me to both come on and pass away more quickly than those of digitalis. I have seen the pressure rise in six hours, and fall in the same time. Cumulative effect, however, here seems very marked. I find, too, that small doses, frequently repeated, have a more powerful effect than the same amount given in one large dose. But our inquiries will not end with drugs acting on tension; there is good ground for hoping they will be extended to other groups; and I look forward to the time when a more complete knowledge of the time during which single doses of most of our medicines act, may give to practical therapeutics a scientific exactness which is now wanting.

THE CROONIAN LECTURES

ON

THE PHARMACOLOGICAL ACTION AND THERAPEUTIC USES OF THE NITRITES AND ALLIED COMPOUNDS.

1893.

In the Croonian Lectures for 1890 Dr. Lauder Brunton set forth with a master's hand the position of our knowledge with regard to the relationship which exists between chemical composition and physiological action. He pointed out the structure of the leading types of organic compounds and explained the influence which both structure and composition have in determining their physiological action.

In the lectures I have the honour of being invited to give my *rôle* will be a more limited one. I propose to take up one of the many series of groups with which Dr. Brunton dealt, and, if possible, add something to our knowledge concerning it.

The Croonian Lectures have been instituted for the promotion of knowledge bearing on the prevention, control, and cure of disease, and in those I am about to give I intend to set forth the pharmacology of the nitrites and some allied compounds, and to show how our knowledge of their actions may be utilised in the treatment of disease. But an essential object of these lectures will be to indicate the influence or physiological action which certain small groups of atoms or molecules of oxygen and nitrogen entering into the composition of the nitrites and allied compounds directly and indirectly exert.

CHAPTER I.

ACTION OF ELEMENTS AND GROUPS OF ELEMENTS.

WHEN a medicinal substance enters into the circulation the molecules of which it is constituted, or those resulting from such chemical modification as it undergoes, come into contact with certain tissues to which they are specially related, and, influencing these tissues, produce the alterations in the function of the various organs which we include under the name of pharmacological action.

Into the cause of the relationship or affinity which seems to exist between the molecules of chemical compounds and the tissues they influence we have not yet penetrated, nor do we know how the ultimate constituents of the tissues are so acted upon that modification of function is produced. But, so far as the chemical compounds themselves are concerned, we have evidence that their effects are in some way the result of the influence of the separate elements or groups of elements of which they are built up, and of the method in which these elements or groups are conjoined.

Some elements make their presence felt pharmacologically in a distinctive manner; the definite effect of others we can hardly determine. It has been shown that many metals—as, for example, potassium, calcium, and barium—exercise a definite influence on muscular tissues of the body. Chlorine, bromine, and iodine have also, as Binz many years ago pointed out, a special action on nerve cells. In O, H, C, and N we have elements the pharmacological offices of which are so wide spread and varied that we cannot at present define their sphere of influence; they, however, unite to form groups of which the specific effect can be distinctly shown. The alcoholic radicles or alkyls, such as methyl, CH_3, tend to give the compounds into which they enter a power of depressing the functions of the higher cerebral centres, and hence producing sleep or general anæsthesia.

The group NH_2, like ammonia compounds generally, has a stimulant effect on the medulla and spinal cord. There are even indications that the small group hydroxyl, OH, has itself a peculiar influence, though probably this influence is wide spread and varied. It must be confessed that our knowledge of the conditions and limits of this influence is of a rudimentary kind. But, imperfect though it is, we owe to it some of the most valuable of the recent additions to the means at our disposal for the prevention, control, and cure of disease, as well as a better knowledge of the way in which some of the older methods may act.

GROUPS CONTAINING OXYGEN AND NITROGEN.

Among the many groups concerning which more information is wanted, are those which contain oxygen and nitrogen. They enter into the composition of many substances used in medicine, and of a still greater number which may be found to have therapeutic value. In these nitrogen is combined with one or more atoms of oxygen.

The table (Frontispiece) sets forth the groups of these two elements to which I propose to call attention.

The formulæ given for these groups and their compounds are founded on their chemical reactions and decompositions, and are those which are generally accepted as representing their structure. The first or nitrite group consists of an atom of triad nitrogen which has two of its affinities satisfied by an oxygen, whilst the third is attached to a second oxygen. The second oxygen atom has thus one of its links left free.

Nitrogen, it is well known, at times plays the part of a pentad element, and it is supposed by chemists to do so in the second or nitrate group. Here four of the affinities of the pentad nitrogen atoms are satisfied by two oxygen elements, whilst to the fifth link is attached a third atom of oxygen which serves to couple the molecule with other groups. In the next or nitro group the nitrogen is also probably pentad, and has attached to it two atoms of oxygen. It will be noted that this group is isomeric with the nitrite group, but owing to the difference in structure, the corresponding compounds into which the group enters have not the same pharmacological, chemical, or physical properties.

In the nitrosamines, as in the nitrite group, we have a triad nitrogen, two links of which are satisfied by an oxygen atom, the third having attached to it a nitrogen element.

It is usual to regard hyponitrites as containing a group, NO, united directly to the other element of the compound, hyponitrous acid being looked upon as HNO, and sodium hyponitrite as NaNO. But the recent researches of Zorn and others, seem to have proved that the acid and its salts are diazo compounds, and I have thus represented them in the table.

The last group, the oximes, consists of a group, NOH, the nitrogen of which is united to a carbon element.

It will be seen that the groups of nitrogen and oxygen given on the list enter into metallic, fatty, and aromatic compounds. I propose, however, confining my remarks almost entirely to the metallic and fatty compounds containing them, and even concerning these the observations I have to record must be regarded as the result of a preliminary investigation only of their properties.

METHODS IN WHICH GROUPS OF ELEMENTS IN COMPOUNDS PRODUCE THEIR EFFECT.

Before speaking of the influence exerted by the groups of molecules to which I have drawn attention, it may be well if I briefly discuss the methods in which they may produce their effects on the tissues. It will be noted that while the compounds into which they enter, nitrite of sodium and nitrate of sodium, for example, have an independent existence, the molecules themselves are not known in a separate form, yet there is evidence that, like the radicles of the fatty series (CH_3, etc.), amidogen (NH_2), and hydroxyl (OH), their special physiological influence can be traced through the various compounds they enter into, modified, of course, by other molecules with which they are associated. The action of the nitrites of the alkaline and earthy metals on muscular tissue will illustrate this.

When the excised muscles of certain animals, such as the frog, are placed in a 0·6 to 0·75 per cent. solution of sodium chloride, the so-called normal salt solution, they continue to live and behave under stimulation in a fairly uniform manner provided they are exposed to exactly similar conditions. If the contractions of corresponding muscles are registered by a myograph, they always yield characteristic tracings, which, though influenced by method of excision, temperature, season of the year, and many other factors, yet correspond in character, provided the circumstances under which the curves are taken are alike. The duration of the life of the muscle too is, if these conditions are fulfilled, much the same.

Fig. 111 represents a muscle curve taken in normal salt solution. As I shall have occasion to refer frequently to the influence on muscle tissue of the substances I am about to speak of in these lectures, I may here take the opportunity of explaining that I have estimated this influence by means of an apparatus devised by Dr. Wild. It is a modification of the instrument originally employed by Dr. Brunton and Professor Cash in their well-known investigations on chemical constitution and physiological action. The excised gastrocnemius of the frog is surrounded by normal salt solution to be tested, and when it contracts from the effect of a break current, the character of the contractions produced is represented in the usual way by a lever writing on the revolving drum.

It is sometimes convenient to estimate the vitality and contractile power of muscles without taking curves. For this purpose contractions are recorded on a stationary drum every few minutes, the drum being moved a short distance between each new contraction. When a frog's gastrocnemius is surrounded by normal salt solution for ten to twenty minutes the curves change but little, then they fall gradually until the death of the muscle in about twenty-four hours. This diagram (Fig. 111), like all the others, is taken by the camera from an actual tracing; for the sake of clearness only a few of the curves have been reproduced.

In Fig. 112 are represented the contractions of muscle in normal saline taken at regular intervals and recorded on a stationary drum for six hours. The muscle was then left in the solution all night. The small contractions at the right hand, taken twenty-four hours after, were produced by the full strength of the induction current, and simply show that the muscle was not then dead.

The influence which the addition of small quantities of alkaline and earthy metals to normal salt solution has on muscular contraction and life has been investigated by Dr. Brunton and Professors Cash and Ringer. Figs. 117 and 120 show the effect of 1 part of barium chloride and calcium chloride added to 1,000 of normal saline on muscles.

Barium chloride increases the contractile power of the muscle, and alters the shape of the curve; it causes, too, contracture, and kills the muscle in three or four hours.

Calcium increases the contractile power of the muscles, and causes contracture, but tends to maintain the vitality of muscle which lives more than twenty-four hours.

That the effect produced on the contractions is not due to increased density of the fluid surrounding the muscle is proved by the fact that 1 in 1,000 of chloride of sodium added to a normal salt solution does not in any way influence contraction or vitality.

Now if we compare these muscle tracings with those produced by the addition of 1 in 1,000 of the corresponding nitrites, we see at once that the nitrite element has a very distinct effect (Figs. 111—122). In this strength of sodium nitrite solution (Figs. 113 and 114) the contractions become less strong, and in about thirty to forty minutes the muscle fails to respond to stimulation, and is dead. If we place a muscle in a 0·75 per cent. solution of sodium nitrite, the muscle dies in 15 to 20 minutes (Fig. 115).

When 1 in 1,000 of barium nitrite is added to the normal salt solution the contractions at first produced by stimulation have the characteristic peculiarity of barium (Fig. 118), but not so well marked as in the case of the chloride. But rapidly, much more rapidly than with the same quantity of chloride of barium, the contracture is annulled. The contractile power decreases, and the muscle dies in 30 minutes. If a smaller quantity of barium nitrite be used, such as 1 in 2,000 to 1 in 5,000 (Fig. 119), the barium contracture may not occur.

If we compare the effects produced on muscle by the same metallic elements with ONO_2, we note a striking difference. Whilst sodium nitrite is a poison causing the muscle quickly to lose its contractile power and vitality, sodium nitrate is in small proportions quite as favourable to the vitality of muscle as is chloride of sodium itself. A muscle in a 0·6 to 0·75 per cent. solution of sodium nitrate will contract as well and live as long as a muscle in normal saline. Strong solutions of the nitrate, like strong solutions of sodium chloride, will, of course, kill muscle quickly.

The difference between the physical properties of nitrite and nitrate solutions of the same metals of equal strengths will not account for the great differences between their physiological effects on muscle and other tissue. It must be due to the action of the acid molecules ONO and ONO_2.

The way in which such molecules as ONO and ONO_2 produce their effects it may not be possible to determine with certainty. Yet the matter is worthy of some consideration. The specific changes which a chemical compound produces in tissues must be due to the influence, chemical or molecular, exerted on the ultimate elements of the tissue (1) by the large molecules of the compound itself, or (2) by new molecules resulting from decomposition of these larger molecules. When complex molecules enter the body they not infrequently undergo decomposition, and their elements are broken up into new groups. When, however, metallic nitrites and nitrates act on muscle tissue we have no absolute evidence that any decomposition takes place. Binz, in speaking of the action of nitrites on the nervous system, has suggested that when nitrates are taken nitrous acid, HNO_2, is set free and decomposed, HNO_3 and NO being formed. He attributes the effects of nitrites on the nerve cells to these products of decomposition, but especially to active oxygen, which he holds is formed.

There is evidence that such changes as he indicates may take place, for in the body HNO_2 is to some extent oxidised and HNO_3 formed, but there is no proof that such oxidation is necessarily the antecedent of the physiological effects on tissue, especially on muscular tissue, which nitrites produce. I have been unable to obtain any indication of the oxidation of nitrites during muscle contraction, and their influence on muscle is in no sense akin to that produced by free acid, the formation of which should precede, or at least accompany, the changes he speaks of.

It seems more probable that the influence exerted by nitrites and nitrates is due directly to the molecules of which they are composed acting on the tissue elements. It is possible for a chemical compound built up of two or more molecules to act in two ways (1) as a whole molecule, the influence being the resultant of the molecules of which it is composed, or (2) each of the molecules may divide partnership, and each may influence the tissues in its own peculiar way, the general result being the outcome, as it were, of two separate actions.

It is probable that in a large number of chemical compounds it is the whole molecule which influences the tissue elements, and it may then produce an effect which is intermediate between the action of each of its constituent molecules and allied to both, or its influence may be quite different to either of them. But there are some grounds, I think, for believing that the constituent molecules of a compound may act separately, and it seems to me the nitrites and nitrates are probably examples of such separate action. The marked individuality and uniformity of the influence of the ONO group in its various compounds, which I have pointed out and shall still further illustrate in other tissues, may, I think, be taken as an indication of this, and the difference I have noted between the action of smaller and larger amounts of some of the metallic nitrites on muscle seems to me to support the view.

If we expose a muscle to 1 in 1,000 of barium nitrite we see, as I have pointed out already, what may be called the barium effect, that is, the prolonged and heightened contraction and contracture; though distinctly less than in the case of barium chloride, it is still at first well marked, but it gradually disappears, the curve becomes smaller, and the muscle dies (Fig. 118). When, however, instead of 1 in 1,000 of barium nitrite we use a smaller amount, say 1 in 5,000, the distinct barium effect on the form of the curve is at times absent, though the muscle dies almost as quickly (Fig. 119).

In the action of calcium nitrite the conditions are reversed.

It will be seen from the curves in Fig. 122 when a small quantity of calcium nitrite (1 in 5,000) is used, the peculiarities of the calcium tracing are preserved, and the vitality of the muscle is scarcely interfered with; in stronger solutions (1 in 500 to 1,000) the nitrite influence overwhelms the calcium influence (Fig. 121). The increase in the height of curve which calcium produces is almost annulled, and we no longer see the effect of calcium in promoting vitality; the muscle dies in four hours, whilst in a similar solution of calcium chloride good contractions can be obtained after twenty-four hours.

It seems to me that the curious difference in kind as well as in degree between the effects of small or large quantities of such compounds of barium and calcium on muscle tissue lends some support, though it may be but slight, to the view that the influence which they and similar compounds exert on tissue may be due to the separate and distinct action of the molecules of which the compound is built up. A difficulty in the way of accepting this view is that we have, as a consequence, to allow definite and specific powers to groups of molecules which we cannot prove actually to exist; whether the difficulty will in any way be bridged over by the theory of "ions," which in the last few years has found increasing acceptance in the chemical world remains to be seen.

Chapter II.

THE NITRITE OR NITROXYL GROUP.

I turn now to the first group on the list of oxygen and nitrogen molecules, the nitrites, or ONO, or, as it is sometimes called, the nitroxyl group. I propose to draw attention to the nitrites of sodium, potassium, calcium, barium, and also to following organic nitrites: Ethyl nitrite C_2H_5ONO, propyl nitrite, C_3H_7ONO, isobutyl nitrite, C_4H_9ONO, and amyl nitrite $C_5H_{11}ONO$—though I shall not of course pretend to give a detailed account of them.

General Characters.

Nitrous acid, HNO_2, itself is not known as a definite compound in a pure state. When nitrogen trioxide, N_2O_3, is passed into cold water nitrous acid is produced. It is formed, too, when metallic nitrites are acted on by weak acids and the organic nitrites yield it in contact with water or its vapour. It is an unstable compound at ordinary temperatures, and decomposes rapidly, nitric acid and nitric oxide being formed.

Nitrite of sodium and potassium are deliquescent salts, neutral or slightly alkaline, and very soluble in water. They are very easily decomposed by dilute acids.

The nitrites of calcium, barium, and strontium are like the alkaline nitrites in these two points.

The double nitrite of cobalt and potassium, or Fischer's salt, is very slightly soluble in water. According to Atkinson, it is more easily decomposed by acids than the other nitrites, but my experiments on this point have not accorded with his. I find it less easily decomposed than the other nitrites.

Ethyl nitrite is a volatile liquid, boiling at 62·6° F. It is insoluble in water at 32·0°, but very soluble in alcohol. When an alcoholic solution is mixed with water effervescence takes place, which is due, not to the decomposition of the ethyl nitrite, but to its separation and escape; a portion of the ethyl nitrite remaining dissolved decomposes, and the mixture at once becomes acid owing to the formation of nitrous acid. The amount of ethyl nitrite remaining in solution varies greatly. I find that when a drachm of a 2½ per cent. solution of ethyl nitrite is added to an ounce of water at least 50 per cent. of the nitrite is at once dissipated.

Dilute acids do not immediately decompose ethyl nitrite. It is probable, however, that they hasten decomposition of nitrite in large quantities of water. The vapour of ethyl nitrite is converted into nitrous acid in the presence of watery vapour.

Propyl nitrite is a volatile liquid, boiling at 110° to 115° F.

Isobutyl nitrite has a still higher boiling point—152·6°. It is a pale yellow liquid, with a fragrant odour.

Nitrite of amyl is a yellow ethereal liquid. It is insoluble in water, and decomposed by contact with water, nitrous acid being set free, but not nearly so rapidly as ethyl nitrite.

ABSORPTION, COURSE, AND EXCRETION.

Nitrous acid decomposes very rapidly, but it is not so quickly destroyed that absorption from the stomach cannot take place when it is taken internally. When absorbed it is no doubt at once converted into an alkaline nitrite, for it can replace carbonic acid in its sodium compounds and convert normal sodium phosphate into acid phosphate, sodium nitrite being at the same time formed.

SODIUM NITRITE.

When mixed with artificial gastric juice and put in an incubator at 30° C., solutions of sodium nitrite are rapidly decomposed and nitrous fumes given off, and all nitrite disappears in about twenty minutes. The same change takes place in the stomach, as is testified by the nitrous eructations which at times follow the administration of sodium nitrite. Probably some of the nitrite of sodium is absorbed as well as some of the nitrous acid produced by its partial decomposition, the relative amounts depending on the acidity of the stomach at the time of administration. Manifestly it very quickly passes from the stomach into the system, for its effects on the circulation are usually distinctly visible in from two to five minutes. A portion of the nitrite taken is excreted in the urine unchanged. I have found it after a dose of 6 grains of sodium nitrite. After smaller doses I have been unable to detect it, but the test for nitrites in the urine is not so delicate as in water, and minute quantities will in acid urine be rapidly destroyed. Whether nitrites are eliminated in the saliva and perspiration, it is not easy to say, since they are sometimes found there normally, but they can certainly be excreted by the stomach after injection into the circulation. Dr. Gamgee informs me that in a dog poisoned by the injection first of small then of large doses of sodium nitrite into the jugular vein, the contents of the stomach examined immediately after death were found by him to give clearly the nitrite reaction with the metaphenylendiamine test. The contents of the duodenum and jejunum likewise gave perceptible nitrite reaction. Probably only a small amount is thus usually excreted; the urine in the dog seemed to contain ten times as much nitrite as the stomach contents. Not a trace of nitrite could be found in the bile, which was also carefully examined. In another dog the contents of the stomach gave a strong nitrite reaction. There can be no doubt, therefore, that the stomach is capable of excreting as well as absorbing nitrites.

It is certain, however, that a considerable portion of the nitrite taken is oxidised into nitrate. Röhmann[1] recovered from the urine as nitrate 46 per cent. of the nitrite of sodium he injected into a rabbit, and in the case of a dog 36 per cent. In what manner and when nitrates are formed from nitrites we can of course only conjecture. Binz suggests that the nitrite is thus broken up.

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[1] *Zeit. f. phys. Chem.*, v., p. 233.

$$3HNO_2 = H_2O + HNO_3 + 2NO.$$

It is possible that such a change takes place in the tissues. Yet, as I have previously said, we have no proofs that it leads to the phenomena observed when muscles are poisoned by nitrites. It certainly seems likely that the contact of unstable molecules like ONO with the ultimate elements of tissue may account for the marked and rapid effects of nitrites on the functions of some tissues. But even if the breaking up of nitrites is connected with activity of function it does not follow that the products of this decomposition are the cause of altered functions.

There seems reason for believing that the amount of nitrate and nitrite excreted does not account for all the nitrite taken, and it has been suggested that reducing agents in the body may convert part of the nitrite taken into ammonia. No proof of this has yet been given, but I find that in blood left to decompose, nitrites are destroyed by the reducing agents developed during decomposition, but no trace of nitrate can be found when the nitrite has disappeared.

ETHYL NITRITE.

Experiments with an incubator and artificial gastric juice render it improbable that ethyl nitrite itself is absorbed from the stomach. If a drachm of a 3 per cent. solution of ethyl nitrite is mixed with artificial gastric juice and HCl at 38° C., nearly all the ethyl nitrite is at once dissipated, but some nitrous acid is formed. In fifteen minutes, if the flask remains corked, there is still a slight nitrite reaction, but this is due entirely to free nitrous acid. It is possible that some of the ethyl nitrite which is set free when a 3 per cent. solution is taken into the stomach may be absorbed, but it seems more likely that the whole of the nitrite element of the ethyl nitrite ingested is taken into the circulation as nitrous acid and combines with the sodium of the blood.

Nitrous acid acts like ethyl nitrite. I gave nitrous acid to two men, and by means of the sphygmograph recorded the effect on the circulation. The next day doses of nitrous ether, containing the same molecular equivalent of NO, were administered to them. The influence on the pulse tracing, both as regards extent and duration, was the same after the nitrous acid as after the ethyl nitrite.

When ethyl nitrite is taken internally in ordinary doses the alcohol set free is probably not in sufficient amount to exert any physiological influence.

AMYL NITRITE.

When taken into the stomach amyl nitrite is probably broken up, but more slowly than ethyl nitrite. How far any undecomposed amyl nitrite is taken into the blood we do not know. From the comparatively slight effects produced by amyl nitrite when taken internally, I am inclined to think but little is absorbed. When organic nitrites are inhaled they act much more rapidly and powerfully. They quickly reach the systemic vessels in an undecomposed state, and the fatty molecule is probably effective, as well as the nitrite molecule.

CHAPTER III.

PHARMACOLOGY OF THE NITRITES.

INFLUENCE OF NITRITES ON BLOOD.

It is probable that nitrites affect more or less all the tissues of the body, but the most distinctive influence is seen on the blood and on the muscles. Dr. Gamgee, in 1868, pointed out the important fact that on the addition of nitrites to blood the colour became brown, and the spectrum altered. He found that these changes were due to the conversion of oxyhæmoglobin into what is now known as methæmoglobin, and showed that this conversion was connected with a locking up of oxygen in the new compound.

Since the presence of methæmoglobin in the blood tends to unfit this fluid for its functions, it is important to consider the conditions under which it is formed by nitrites, and destroyed.

In blood outside the body, 1 part of nitrite to 500 of blood causes methæmoglobin to appear at once. With 1 in 1,000 I have found it in three or four minutes, with 1 in 10,000 after a few hours, but it is not in sufficient quantity to be detected by the spectroscope with so small an amount of nitrite as 1 in 20,000.

According to Hénocque,[1] injection of a few centigrammes of a nitrite of sodium solution into the peritoneal cavity of an animal causes methæmoglobin to appear almost immediately, and its effects are well marked in a minute, but after subcutaneous injection not for three to twenty minutes. Given by the stomach, the blood changes are still more slowly produced.

In man, 10 to 12 grains caused in one case blueness of the lips, doubtless due to the production of methæmoglobin, but I find no record of cyanosis caused by a small single dose. To many healthy people I have given 2 to 4 grains of sodium nitrite, to a few 5 to 6 grains; to many, too, I have given 1 to 3 drachms of a 3 per cent. solution of ethyl nitrite, but I have never seen any indication that the production of methæmoglobin has followed, nor have I seen it produced by similar doses in cardiac or pulmonary dyspnœa or other ailments in which I have used the nitrites, notwithstanding that I have given 2 to 3 grains of sodium nitrite every two or three hours, and as much as 5 drachms of ethyl nitrite solution within an hour. I find, however, a case recorded in which after a drachm of nitrite of ethyl solution given every three hours in an asthmatic subject, there was an appearance of cyanosis after the fourth dose, which is said to have passed away after the drug was discontinued. It is by no means certain that the cyanosis in this case was due to the nitrite given.

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[1] *Comp. Rendu. de Biol.*, v., p. 669.

Methæmoglobin in the circulating blood of living animals, unless in large quantities, is quickly disposed of. Hénocque produced methæmoglobin in rabbits by injecting various quantities of sodium nitrite, and by frequent examinations of blood from the ear determined the time of its disappearance from the blood. He finds that the methæmoglobin, once produced, continues for a time varying from fifteen minutes to an hour and a half. Doubtless, however, it often exists a much longer time. After large quantities of nitro-glycerine had been introduced into the stomach of a dog, methæmoglobin was found in the blood for two days.

Hénocque thinks that the methæmoglobin may be transformed into oxyhæmoglobin in the respiratory processes. In blood outside the body methæmoglobin is not transformed into oxyhæmoglobin till putrefaction sets in, but it seems probable that the contact of methæmoglobin with living tissues causes this transference. Dr. Gamgee has sent me an interesting record of an experiment he has made which bears on this subject. He tied one aorta of a frog, and inserted into the other a cannula connected with a reservoir containing 1 part of defibrinated calves' blood and 10 of normal salt solution in which methæmoglobin had been produced by the addition of $\frac{1}{75}$th of its volume of a 1 per cent. solution of nitrite of amyl. Into the sinus venosus he fixed a cannula, which was connected with a flattened glass tube allowing of spectroscopic examination of blood flowing through it. The heart pumped blood by which it was fed from the reservoir through this glass tube, and hence, by an india-rubber tube back into the reservoir, continuous circulation of the methæmoglobin blood through the heart thus taking place. Within an hour he found that the blood seemed brighter and the methæmoglobin band less distinct. In twelve hours these changes were still more marked. In twenty-four hours the methæmoglobin band could not be detected, only the oxyhæmoglobin bands could be seen. The heart continued to work vigorously, the beats, which under the influence of methæmoglobin blood had fallen from 8 to 5·5 in 15 seconds, having again risen to the original number. This experiment seems to show that in contact with living tissues methæmoglobin is easily converted into oxyhæmoglobin, the nitrite doubtless disappearing at the same time, and it is evident that methæmoglobin does not interfere seriously with the power of blood to nourish the heart muscle.

Outside the body sodium nitrite seems to have no effect on the form and size of the red corpuscles. From what has been stated it is manifest that we have no cause to fear the production of methæmoglobin or injury to the blood from the medicinal administration of nitrites.

Influence of Nitrites on Skeletal Muscle.

With regard to the skeletal muscle tissue, I have already indicated the nature of this action. The presence of ONO molecules in striated muscular tissue tends to decrease the contractile power and the duration of vitality. A solution containing 0·75 per cent. of sodium nitrite kills a muscle in 15 minutes, but at first it powerfully irritates it, causing spontaneous contractions. A weaker solution, 1 in 1,000, quickly diminishes the contractile power of muscle, and causes it to die in thirty to forty minutes. The same strength of potassium nitrite kills muscle even more quickly, for the potassium element is also injurious. Sometimes it appears as if a primary stimulation effect is produced at least in the muscle tissue of the frog. In a series of observations made in June, July, and August, this effect was a rare occurrence, whilst in another series, in April and May, it was almost always seen, and was found to commence within a few minutes after exposure of the muscle to the nitrite solution. It lasted about fifteen minutes, after which the muscle rapidly died.

A muscle exposed to 1 in 5,000 of sodium nitrite can only be made to contract for about two hours, and is so injured by a strength of 1 in 6,000 that it dies in four hours; but 1 in 20,000 seems to have hardly any toxic effect, its contractile power continuing after exposure to this strength for twenty-four hours. It is worthy of remark, however, that the alteration in the function and vitality of muscle caused by sodium nitrite decreases and passes away with great rapidity, as the nitrite in contact with the fibre is lessened in quantity or removed.

I do not intend to notice in detail the influence of the organic nitrites, for saline solution containing these compounds at once becomes acid from their decomposition. When, therefore, muscle is immersed in normal saline solution containing them, it is impossible to say how far the phenomena observed are due to the free acid or to the nitrite itself. I may point out, however, that 1 in 1,000 of amyl nitrite in saline solution is fatal to a muscle in forty minutes, or in about the same length of time as sodium nitrite, but it produces a certain amount of contracture, and I found the contracture still present, even when, by the addition of a minute quantity of soda, the fluid was kept as nearly as possible neutral.

ACTION ON INVOLUNTARY MUSCLE.

On involuntary muscle, both in cold-blooded and warm-blooded animals, nitrites have a powerful paralysing effect. This can be shown by perfusing alternately a pure saline solution, and one containing a small quantity (1 in 1,000) of a nitrite through the vascular system of a tortoise after decapitation. When saline is perfused a fairly equal flow is soon established; when the saline containing nitrite is passed through, the flow is considerably increased, often to the extent of 100 to 200 per cent. This increase can only be due to relaxation of the vessel walls. When the nitrite saline is replaced by pure saline, the vessels contract again, and the flow becomes less. The further perfusion of nitrite saline again increases the flow, which will again decrease with normal saline.

What part the peripheral ganglia play in the dilatation of the vessels cannot be ascertained, but there are grounds for believing that the nitrite influence exercised is largely on the muscle tissue itself. I have found 1 in 10,000 quickly double the flow through the vessels of the tortoise, and Atkinson[1] says he has seen 1 in 100,000 increase the flow 16 to 18 per cent.

One in 1,000 of nitrite of sodium will usually increase the flow by from 50 to 200 per cent.

The dilatation of the vessels in warm-blooded animals may be shown by passing through excised portions first pure blood and then blood containing nitrites.

When a solution containing 1 in 1,000 of sodium nitrite is passed through the kidney vessels, the increased blood flow is sometimes enormous, amounting to 200 or 300 per cent., and the same is the case when a similar solution is passed through the hind quarters of an animal recently killed. In both cases the vessels contract, and the flow diminishes when the nitrite is replaced by normal blood, and is increased again when nitrite blood is perfused.

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[1] The Pharmacology of the Nitrites and Nitro-glycerine, *Journ. of Anat. and Phys.*, vol. xxii. I desire to express my indebtedness to this most valuable paper for many of the facts set forth in these lectures. With one or two slight exceptions my experiments have entirely confirmed those of Dr. Atkinson.

The group ONO then seems to have a very powerful effect in causing temporary paresis of the muscular structure contained in the arterial walls, and hence dilatation of the walls. As is the case with the skeletal muscles, the effect of the nitrite ceases at once when it is removed from contact with the tissue by washing through with pure blood, and no evil effect is left behind. I believe this to be an important point to bear in mind in the therapeutic use of the nitrites. I pointed out that a preliminary stimulation was not infrequently observed when the gastrocnemius of a frog was exposed to a very weak solution of sodium nitrite. I have not seen evidence of such primary stimulation of the contractile tissue of the vessels under smaller quantities of the nitrites, but I have seen contractions occur in the vessels of a tortoise with a 0·75 per cent. solution, and here the subsequent perfusion of normal saline raised the flow perhaps by diluting the nitrite poison in the vessel walls.

The influence of the nitrites of potassium, barium, calcium, and strontium I have only tested on cold-blooded animals. Potassium itself acts in the same direction as the nitrite group, that is, it dilates the vessels; chloride of potassium, for example, in dilute solutions always causes an increased flow through the vessels. It would be expected, therefore, that nitrite of potassium would, other things being equal, dilate the vessels of an animal more than sodium nitrite, and this, on the whole, I have found to be the case; but in barium and calcium we have metals which cause contraction of the vessels, and antagonise the influence of the group ONO. The result of this antagonism resembles somewhat that which has been described as taking place in the gastrocnemius of the frog. When relatively strong solutions of barium nitrite are used marked contraction occurs; with weaker solutions it is slight, or there may even be dilatation.

The calcium element almost antagonises the ONO group; relatively strong calcium nitrite solutions show temporary contraction like the barium, though it is less marked. Nitrite of ethyl is so rapidly converted into nitrous acid and alcohol when it comes in contact with water that it is impossible to determine its influence on vessels. It only dissolves in saline solution with the aid of a little alcohol, and so much acid is produced by its decomposition that 1 in 10,000 or any stronger solution causes distinct contraction of the vessels. Dilatation follows the circulation of 1 in 30,000, but this may be due to the faint acidity of the solution, since very dilute acids are said to dilate vessels, though stronger acids contract them.

Amyl nitrite is only soluble in saline solution when a small quantity of alcohol is added, but the presence of a quantity of alcohol sufficient to dissolve 1 in 10,000 of amyl nitrite does not influence the vessels. I find that whilst 1 in 10,000 sometimes contracts and sometimes dilates vessels, a stronger solution always contracts them. A weaker solution, 1 in 20,000 to 1 in 30,000, dilates them temporarily. It is impossible to eliminate the disturbing influence of the acid which is developed when amyl nitrite comes in contact with water.

We have some evidence that nitrites act on involuntary muscular fibre in other parts in the same manner as they act on that which surrounds the vessel walls.

Mr. Cook, in some experiments made under Professor Stirling's directions in the Physiological Laboratory of the Owens College, has shown that 1 part of sodium nitrite to 1,000 of saline causes diminution of the spontaneous contraction, which naturally takes place in the circular fibres of the frog's stomach, and rapidly paralyses the muscle. Atkinson, too, finds that a 1 per cent. solution destroys the contractility of the intestinal muscle to the electric current in thirty to forty minutes, but after exposure to 1 in 1,000 for three or four hours contractions could still be obtained.

Atkinson has also proved that muscular tissue in the ureter dilates under the influences of nitrites of sodium. If a rabbit be killed, and placed in a hot chamber, and normal saline run through the ureter, dilatation of a marked character occurs.

ACTION ON THE HEART MUSCLE.

It can be shown that the action of nitrites on the heart muscle of the frog is much the same as on the contractile tissues of the vessels.

In the apparatus devised by Professor Roy it is possible to determine the action of a drug on the muscular tissue of the heart alone. On feeding the ventricle with a saline solution from a reservoir placed above it, it contracts after a while regularly, and continues to do so for a long time; on allowing a saline solution[1] containing a definite quantity of a substance to be tested to pass through the ventricle, modifications in the frequency and form of the heart's contractions will indicate the pharmacological activity of the substance, so far as the muscle wall is concerned. The tracings I give represent the average effects produced.

Now it is found that liquid containing 1 part of sodium nitrite in 1,000 of saline solution first quickens the action of the heart for two or three minutes, decreasing, however, the force of each contraction, but afterwards the heart beats more slowly as well as less powerfully, and in ten minutes stops in diastole. One in 5,000 also quickens the heart's beat for a few minutes, and slightly weakens it; then it slows it, but the heart will continue to live for two hours. One in 10,000 quickens and weakens the heart for twenty minutes, but in other ways it has very little effect.

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[1] By saline solution, I mean in the case of a heart a 0·6 per cent. solution of chloride of sodium, containing also a minute amount of potassium and calcium, as recommended by Dr. Ringer.

When the nitrite is replaced by a saline solution the heart begins beating anew, and soon regains entirely, or almost entirely, its previous vigour. It is possible to start and stop the heart two or three times by alternately using a saline solution and a saline solution containing 1 part in 1,000 of nitrite. The diagram (Fig. 123) illustrates the influence of sodium nitrite on the muscular tissue of the heart.

In no case have I found any actual increase in the force of the individual heart beats. Potassium nitrite acts like sodium nitrite, only the weakening effect is more marked.

When a molecule of calcium instead of a molecule of sodium is combined with the ONO group, a slightly different effect is produced. With 1 in 1,000 the action is much the same as with sodium nitrite of the same strength, except that the quickening is not so great. With 1 in 10,000 there was also very little quickening; the beats are squarer at the top. Calcium, as Professor Ringer has shown, prolongs the systole, and thus renders the top of the beats squarer—that is, as Professor Ringer has shown, it tends to prolong the heart's action. Here, as is usual in the lime compound with ONO, the effect of the calcium is best seen when a very dilute solution is used.

One in 1,000 of barium nitrite at once shortens the height of contraction, and kills the heart rapidly. When the heart is fed with 1 of barium nitrite in 2,000 of saline, the duration of systole is so much increased that full diastole does not occur, but soon the action of the heart is quickened and weakened. Eventually the barium nitrite acts as a poison to the heart. Fig. 124 illustrates this.

The rapid decomposition which amyl nitrite undergoes prevents its effects on the heart being determined, and in saline solutions even small quantities cause the fluid to become acid. When blood is used, however, the fluid does not become acid, and the influence of amyl nitrite on the heart muscle can be determined. Fig. 125, taken with Kronecker's apparatus, shows well the influence of amyl nitrite on the heart muscle.

It will be seen that by 1 in 4,000 of blood the beat of the heart is quickened; and though the height of the contractions is less, there can be little doubt that the heart does more work. When a larger quantity of amyl (1 in 2,000) is present, the contractile power of the heart is decreased, and the heart beat becomes slower. A still larger amount stops the heart in diastole.

The outcome of experiments on the heart muscle is as follows. The molecules of the ONO group in whatever combination, when present in even small quantities, tend to quicken the contractions but to weaken them. If the solutions coming in contact with the heart are very dilute, the quickening may make up for the weakened action, and the heart probably does as much, it may be more, work for a short time. Stronger solutions containing compounds of ONO, after quickening, weaken, slow, and arrest the heart's contractions. But susceptible though the heart is to the influence of nitrites, the evil influence is very evanescent if the nitrite molecules be removed.

INFLUENCE OF NITRITES ON THE NERVOUS SYSTEM.

The nitrites depress the functions of the nerve centres and nerves, but not to the extent which might be expected from their influence on the muscles, vessels, and heart. When given in toxic doses they cause, in both cold and warm-blooded animals, heaviness and apathy. In man, too, cerebral depression has been seen after toxic doses. Inhalation of the vapour of nitrous ether has been followed by stupor, and after nitrite of amyl in large quantities loss of consciousness has occurred. Such effects are probably due to the direct influence of nitrites on the cerebrum.

I have never seen a narcotic influence exercised by medicinal doses of the nitrites, but drowsiness after nitroglycerine, which acts like the nitrites, has been recorded.[1] This may be the outcome of the circulatory disturbance it causes; certainly no narcotic effect has to be feared from the use of nitrites. The sense of distension and throbbing in the head, the dizziness and the headache felt by some after amyl, ethyl, or sodium nitrites are manifestly due to circulatory changes; but the prolonged headache, which does not come on always immediately, but may last for twelve hours or more after some nitrites have been taken, is probably not due to the same cause. It is most frequent after amyl and isobutyl compounds. I have felt it myself after both, and also after propyl compounds, but not after ethyl nitrite or sodium nitrite. I am inclined to think it is caused by the alcoholic radicles, and not by the nitrite element, for other amyl, isobutyl, and propyl compounds produce the same kind of long lasting headache.

Convulsions in the lower animals are rare after nitrites. They are said to have occurred in man after the injection of amyl nitrite.[2] I once saw twitching of the eye muscles accompany a syncopal condition which followed on the administration of nitrite of amyl. Brunton, too, alludes to the occurrence of a slight convulsive attack after the same drug. It seems likely that such attacks are connected with syncope or slight asphyxia rather than with a direct action of the drug on the brain, and considering the rarity of cerebral disturbance after any of the nitrites, and the entire absence of fatality when they have appeared, we may, I think, safely conclude that, though the nitrites may cause some unpleasant symptoms, yet their influence on the cerebrum is no bar to their use even in full medicinal doses.

The functions of the cord as well as of the muscles are in frogs depressed by nitrites, both its reflex and conducting power being diminished, the latter, according to Atkinson, much more slowly than the former. Dr. H. Wood says that the diminution of reflex activity caused by amyl nitrite is never preceded by functional excitement. In man other symptoms so far predominate that even from toxic doses no distinct indication of an effect on the spinal cord has been noticed.

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[1] Murrell: *Nitro-glycerine as a Remedy in Angina Pectoris*, p. 17.

[2] Strahan, *Journ. Ment. Sci.*, xxx., 252. There is some doubt if these convulsions were altogether due to the injection.

We have no proof that the motor nerves are markedly influenced by the nitrites; nor are the nerve endings especially affected by them; at least, it can be shown that they are not more powerfully depressed than are the muscles. On exposing a muscle to a solution of 1 in 1,000 of sodium nitrite, and recording the contractions produced by stimulation of the muscle and nerve alternately, I find that the relative effect of the strength of stimulation is continuously maintained until the death of the muscle. (See Fig. 116). No evidence has been given that even in toxic doses sensory paralysis is produced, or that the application of sodium nitrite paralyses the sensory nerve endings.

To determine whether it possesses any analgesic influence other than that which arises from its effect on the circulation, I have tried it locally and generally for the relief of pain. Locally applied I have not found it possess the slightest soothing influence. I have given it internally in doses of from 3 to 5 grains for the relief of pain in various ailments, but save in the case of pains of an anginal character, in headache, and very rarely in neuralgia, I have never found it of the slightest benefit. In all cases in which it was given with relief there have been grounds for thinking that the disappearance of the pain may have been due to circulatory changes or to suggestion. It has failed to relieve pains where the other analgesics have succeeded. A few cases are indeed recorded in which the local application of nitrite of amyl and nitro-glycerine are said to have removed the pain of toothache, and many where these drugs have relieved headache and neuralgia, but such ailments are so capable of relief by vascular alterations and mental influence that we cannot, in the absence of other indications, infer from their relief that amyl nitrite has a direct analgesic influence.

GENERAL INFLUENCE ON THE CIRCULATION.

I have already alluded to the action of nitrites on the contractile tissue of the vessel walls and on the heart muscle, but the general influence on the circulation requires further notice. The most important feature of this influence is the lowering of arterial tension. Dr. Brunton[1] in 1870 showed that the lowering of tension was due to dilatation of the blood vessels, and from the fact that this dilatation occurred even after section of the cord, he came to the conclusion that the nitrites act on the muscular walls of the arterioles, influencing the muscle fibre directly, or through the local ganglia. This view was controverted by Filehne[2] on the ground that section of the sympathetic interferes with the vascular dilatation produced by the nitrite, and by Bernheim[3] because after arterioles are dilated by amyl nitrite, they may be made to contract by vasomotor stimulation.

The Experiments of Meyer and Friedreich[4] supported the views which Brunton had expressed; they found that when the effect of nitrite of amyl is restricted to the brain it does not bring about a fall of pressure. The dilatation of the vessels by nitrites when the brain and spinal cord have been destroyed, and in separated organs, which can only result from their influence on the vessel walls, is of course much in favour of the view that they lower tension by their action on the peripheral vessels; and Cash[5] has advanced further evidence that the effect of nitrite in reducing tension is the result of its action on the vessels. Like Meyer and Friedreich, he finds that nitrite of amyl produces no effect on the circulation when its influence is restricted to the brain; but he has further shown that if the head of an animal be cut off from the circulation, inhalation of pure amyl nitrite causes a rapid fall of pressure, which cannot therefore be due to influence on the vasomotor centre. He also points out that after reduction of tension by division of the splanchnic nerves, the nitrites cause a further fall of pressure.

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[1] *Journ. Anat. and Phys.*, vol. v., p. 92.
[2] *Pflüger's Archiv.*, vol. ix., p. 470.
[3] *Pflüger's Archiv.*, vol. viii., p. 253.
[4] *Archiv. f. ex. Path. und Pharm.*, vol. v., p. 55.
[5] *Proceedings Royal Soc.*, 1891.

Besides reducing the tension, the nitrites usually quicken the pulse, and this quickening is generally accompanied, if the dose be small, by such an apparent increase in force as to give the impression that a stimulant effect on the heart has been produced, for the pulse feels fuller and more distinct. Yet experimental evidence indicates that nitrites do not strengthen the actual force of the heart's beat, and that they are capable, even in comparatively small amounts, of weakening the cardiac contraction.

The question whether nitrites are, as Dr. Reichert[1] strongly maintains, real cardiac stimulants or not is an important one, for we find nitrites recommended not only where tension is high and relief might be expected from drugs which lower it, but in syncope, heart failure from chloroform, and other conditions in which a stimulant is indicated rather than a tension reducer, and in which any drug which greatly depresses the heart might produce serious consequences.

It may be well if I state the main facts concerning the effect of nitrites on the heart which bear upon this question. As I have shown, nitrites in the isolated frog's heart cause acceleration of beat for a short time, though the contractions are rendered somewhat less powerful and afterwards slower. Atkinson employed 1 of nitrite to 10,000 of blood, and, using Williams' apparatus, noticed a rise in pressure for some minutes, which he attributes to a quickened action of the heart; it was followed by a slow fall and death in forty to sixty minutes.

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[1] Reichert: (*Am. Journ. of Med. Sci.*, July, 1880, p. 168).

With 1 in 20,000 the rise due to quickened action lasted ten to fifteen minutes. In no case has any actual increase in the force of the heart's contraction been observed. But the total work of the heart may be augmented by the increased rapidity of beat. We may presume that a quickening of the heart's action similar to that in frogs takes place in mammals from the direct action of the nitrite on the heart muscle, but here a further quickening is produced by the paralysing influence which nitrite can be shown to exercise on the vagus centre. In mammals, then, as in frogs, no evidence has yet been obtained that the individual beats of the heart are strengthened by nitrites, although at first, acting more rapidly, it may do more work in a given time. But the increase in rapidity does not make up for the weakened muscular power and dilatation of the vessels, and the tension falls. Only one observer, Reichert,[1] records a slight rise in tension after the introduction of nitrites into the circulation, and this for not more than half a minute.

If, as experiments seem to show, the effect of nitrites is only to quicken the heart's action and not to increase the force of its individual contractions, how are we to account for the markedly greater distinctness of the pulse which is so often noted after nitrites, and for the increased height in the upstroke—the so-called "percussion wave"—of the tracing which is almost invariably seen after small doses of nitrites? Probably two causes contribute to this: (1) Owing to the dilatation of the arterioles, the collapse of the artery is more complete after a dose of nitrite than before it, and the difference between systole and diastole of the artery is more marked both to the finger and in the tracing. (2) The radial artery undergoes greater dilatation owing to the relaxation of its walls under nitrite influence. The pulse, therefore, becomes larger during systole, and the difference between the calibre of the artery in systole and diastole being augmented, it is felt to be more distinct and more full.

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[1] Reichert (*Am. Journ. of Med. Sci.*, July, 1880, p. 170).

Pick many years ago suggested that arterial dilatation might in a reflex manner give rise to increased force of heart beat. If this were the case, we ought to find in the manometrical tracing taken from the carotid of a dog under the influence of a small dose of sodium nitrite that the fall in tension is accompanied by an increase in the excursions, corresponding to the individual heart beat; but this is not so, and until we have more evidence we must conclude that though the heart may do more work in a given time, the force of the cardiac contractions is not increased by nitrites.

Although we have no proof that nitrites will increase the force of the heart's beat, we have experimental evidence that they are competent to weaken it, and faintness is occasionally complained of after nitrites. The inhalation of amyl nitrite and large doses of sodium and ethyl nitrite are capable of producing it.

On one occasion I myself suffered from a very marked syncopal attack after taking a large dose of ethyl nitrite. Whilst my tracing was being taken I suddenly felt faint, the heart beat became slow and the excursion smaller; then a prolonged intermission occurred and faintness compelled me to lie down; the slow beat continued for some minutes after the faint feeling had disappeared.

I may mention, in passing, a curious result which followed from publishing in the *British Medical Journal* a warning with regard to this effect, without stating that I was myself the subject of the experiment. A year or two after the record appeared, an anonymous novel was published, purporting to show that in consequence of vivisection being allowed, hospital physicians and surgeons experimented upon their patients in a horrible manner;

and subsequently an appendix, called "Dying Scientifically" was issued, giving the sources from which had been culled the heart-rending illustrations of the barbarity of hospital physicians and surgeons with which the novel was filled.

Lighting accidentally upon this book some time afterwards, I was amused to find that the experiment upon myself was one of the bases of the attack made on hospital physicians and surgeons. "Who," it was asked, "were the patients on whom such experiments were tried; and where were they found if not in the . . . Infirmary?" And so the trial of the drug on myself was put down as proof of the dangerous experiments made by hospital doctors upon their patients. This is but another example of the way in which anti-vivisectionist writers get at the "facts" wherewith they try to influence the public mind.

I have never myself seen any tendency to syncope after 3-grain doses of sodium nitrite, although I have given this amount extensively. It has, however, been known to occur after this and larger doses.

In deciding whether the nitrites can play the part of cardiac stimulants, it is well to bear in mind the resemblance and differences between their action on the circulation and that of alcohol. Both dilate the vessels. Alcohol, like the nitrites, increases the frequency and—to the finger—the force of the pulse; but though experimenters are not agreed as to whether it increases either the power of the heart's contraction or the amount of work it does, all hold that alcohol in large amounts decreases the heart's power. In these points there is considerable likeness between the action of alcohol and that of the nitrites. The difference between the two seems to be that the nitrites are far more rapid and seemingly more evanescent in their action. They quicken the beats more markedly, and dilate the vessels more quickly and completely. They far more readily depress the action of the heart. On the whole, it seems to me we must accord to nitrites in small doses a certain degree of that kind of stimulating power which we attribute to alcohol, but it is exercised much more quickly, passes away more rapidly, and is far more readily followed by decreased cardiac power than is alcohol.

There are several points of considerable practical interest to be noted with regard to the effects of nitrites on the tension and the rate of the pulse and on the regularity of the heart beat. The influence of nitrites in the relief of disease is closely associated with, if not dependent on, its tension-reducing powers. It is important, therefore, we should know how quickly the effects of the various nitrites on tension are produced, and how long we may expect them to last.

Changes in arterial tension are not often indicated by subjective phenomena, and their extent and duration can only be measured by the sphygmograph. With this instrument I have tried by means of tracings taken frequently to estimate the time at which it reaches its lowest point and its duration.

The influence of amyl nitrite on the pulse commences a few seconds after inhalation. (Fig. 131). The tension is reduced to its lowest point in 40 to 60 seconds, and remains extremely low for 30 or 40 seconds, the pulse waves being reduced in size and sometimes irregular. Then it rises again, occasionally suddenly, and in a minute and a half to two minutes it is only a little lower in tension than it was before the inhalation. This slight lowering may continue for several minutes. Isobutyl and isopropyl (Fig. 129) nitrites when inhaled act almost like amyl nitrite.

Sir B. W. Richardson, to whom we are so much indebted for knowledge concerning amyl nitrite, has drawn attention to the fact that when amyl nitrite is taken internally its effects are much slighter, though more prolonged, than when inhaled. Instead of the tension falling at once and recovering in two minutes, it falls gradually for usually twenty to twenty-five minutes, remains low a short time, then rises to its normal height an hour to an hour and a half after the dose has been taken. (Fig. 132). Because amyl nitrite is such a powerful agent when inhaled, one drop is regarded as the proper dose, but this is a mistake; 3 to 5 minims may be required to produce about the same effect as that which follows 2 grains of sodium nitrite.

A small dose of sodium nitrite (2 grains) distinctly affects the pulse in two or three minutes, the point of lowest tension is usually reached in eight to forty minutes, and distinct influence on tension ceases in from one to three hours. (Figs. 126—127). Ethyl nitrite has much the same effect, and on the whole lasts as short a time. (Fig. 128).

I shall not here allude to the action of other metallic nitrites, since, with the exception perhaps of the strontium salt, they are unlikely to prove useful remedial agents. The combination of cobalt with potassium I once thought might prove useful, but its effects are unreliable, because its decomposition is so greatly modified by the condition of the stomach.

I have used the term duration of action to signify the period between the time the drug is taken and the time at which the tracing first becomes normal, but this may not be the real limit of the action of nitrites on the vascular system. It is quite possible that some vessels, as for example those of the brain, may continue dilated after others have assumed their normal condition.

After the tension becomes normal it sometimes falls again slightly, and I have noticed small oscillations in tension for a short time. How long they last I do not know, for they merge gradually into those minor differences which are observed in normal pulse tracings. For practical purposes we may look on the influence of the nitrite as ended when the pulse first reaches its normal tension.

The following table gives a general idea of the influence on pulse tension and frequency of the two nitrites and nitroglycerine in small doses. Four observations on each drug have been selected from a large number to illustrate the variations which occur in their action.

—	Dose.	Action Commences.	Tension, Lowest.	Duration.	Rapidity of Pulse.					
					0.	10 Mins.	20 Mins.	30 Mins.	60 Mins.	120 Mins.
	Grs.		Mins.	Mins.						
Sodium Nitrite	2	2 Mins.	35-70	155	66	81	—	90	87	78
	2	3 ,,	8-40	170	66	74	75	75	68	63
	2	4 m. 40 sec.	16	75	84	90	98	92	92	70
	2	3 Mins.	17-85	175	78	96	100	93	81	74
	Drm.									
Ethyl Nitrite (2½ p. c. solution)	1	1 ,,	18-30	116	66	72	—	75	69	66
	1	2 ,,	15	70	75	75	78	75	75	—
	1	5 ,,	15-50	115	81	87	87	92	78	—
	1	3 ,,	15	80	69	75	75	—	69	—
	Grs.									
Nitro-Glycerine	1	2 ,,	5-20	50	84	84	78	78	84	74
	1	1¼ ,,	3	105	69	72	69	72	64	—
	1	40 Secs.	3-6	80	70	68	72	72	74	57
	1	1½ Mins.	2-45	170	72	66	63	66	60	68

It has been suggested that after the lowering of tension by the nitrites, reaction may occur and the tension may rise above the normal. Though I have looked for such rise I have found no distinct evidence of it.

Many conditions influence the amount of fall in tension and its duration. In people with high tension pulses the fall is less in degree and duration than in those with a circulation of low tension; in those who constantly take nitrites the influence of the drug on the circulation, though not lost, is distinctly lessened.

Though people vary very much in susceptibility, I have never seen anyone entirely unaffected by such a dose as two grains of sodium nitrite or the inhalation of amyl nitrite; but when the tension is very high, and sometimes during dyspnœic attacks the effect may be very slight.

The administration of 10 to 15 grains of bicarbonate of soda with the nitrite delays the appearance of decided lower tension for a few minutes (6 to 10) and seems to lengthen somewhat the time during which the drug acts.

A point of great interest in the action of the nitrites is the minuteness of the amount which will affect the circulation; one-sixteenth of a grain of nitrite of sodium produces a distinct effect on the pulse in most people.

The effect on the circulation does not increase so much as we should expect with the size of the dose. Two grains of sodium nitrite of course lower the tension more and for a longer time than $\frac{1}{16}$th grain, yet the influence is not proportionate to the difference in dose. Four to six grains, again, lower the tension a little more, and sometimes for half an hour longer, than two grains, but here again the effects are not in proportion to the increased size of dose, and they commence no earlier.

The cause of the difference between the action of amyl nitrite when inhaled and when taken by the mouth probably depends upon the fact that, when inhaled, the whole nitrite of amyl molecule comes at once in contact with the vessel walls in the systemic system. Now amyl in very small doses dilates the vessels as a nitrite does, and quite possibly the amyl molecule accentuates the action of the nitrite molecule. Cash finds that the composition and constitution of the fatty molecules has a distinct effect on the tension reducing power of the corresponding nitrite.

The quickening of the pulse after amyl nitrite is very marked, a rise from 20 to 30 beats being common. After nitrite of sodium and nitrite of ethyl in small doses, there is usually slight quickening, but it is not always present. It is very difficult, however, to estimate the influence of a drug on the rapidity of the pulse, since the frequency of the heart's action is so easily influenced by slight circumstances. A decreased frequency of the pulse is sometimes seen after nitrites, but this, with small doses at least, is never considerable. After poisonous doses, marked slowing of the heart has been in some cases noted. This may be due to the direct influence of the drug upon the heart. It will be remembered that nitrites render the beat of the isolated heart slow, after first quickening it.

Irregularity of the heart's action has been observed after the administration of nitrites, and in a few cases extreme irregularity has been reported after large doses of sodium nitrite and inhalation of amyl nitrite. Using small doses of the sodium compound, I have never seen any marked irregularity result. In two or three instances out of forty or fifty in which the pulse has been watched carefully for many hours after sodium or ethyl nitrite, slight intermission and irregularity have occurred, which had not been recorded before the nitrite was given. Slight irregularity of the pulse is common after the inhalation of amyl, isobutyl, and propyl nitrite.

On the other hand, I have met with at least four cases in which an irregular action, fairly marked before the administration of nitrites, became distinctly less or disappeared entirely when nitrites were given. I have never seen it seriously increased, and I am quite sure the irregularity of the pulse is no bar to the administration of nitrites when for other reasons they are called for. Amyl nitrite markedly dilates the vessels of the face, neck, and upper part of the chest, but evidence of its cutaneous influence is not usually seen in other parts of the body.

Flushing of the face is not common after either sodium or ethyl nitrite, yet in some cases it occurs to a slight extent, and in one exceptional case I have known a slight diffused redness over the body as well as the face follow 3 grains of sodium nitrite.

INFLUENCE ON RESPIRATION.

Amyl and alkaline nitrites in the lower animals first increase the depth and frequency of the respiratory movements, though toxic doses paralyse respiration before the heart ceases to beat. We may assume, then, that medicinal doses will tend to stimulate respiration, so far at least as the respiratory centre is concerned. The manner in which the nitrites affect the pulmonary circulation requires further consideration. To ascertain the state of the pulmonary circulation after amyl nitrite, Filehne[1] made an opening in the chest wall, leaving the costal pleura, which in the rabbit is very translucent, intact. On giving nitrite of amyl he saw no congested condition of the lung, and came to the conclusion that the lung vessels are not affected by this drug. From this it would follow that the vessels of the lung are not influenced by a nitrite like those of the kidney, skin, and extremities. To determine whether this is so or not, a cat was killed by chloroform, and immediately after death placed in a warm chamber; the chest was then opened, and an inflow tube fixed in the pulmonary artery, and an outflow tube in the left auricle. The inflow tube was connected with two reservoirs of blood, to one of which 1 part in 4,000 of nitrite of sodium had been added to pure blood, and the pure and nitrite blood were allowed alternately to pass through the lung tissue, the effluent blood from the pulmonary veins being measured by means of the tube placed in the left auricle. The pressure in the lungs was kept constant by attaching a tube on the trachea to a manometer and air reservoir. (Fig. 134).

It will be seen from the diagram that whilst the rate of flow with normal blood was 2½ c.c. per minute, directly sodium nitrite was introduced an increase to 5 c.c. took place. On continuing the perfusion of the nitrite a rise to 27 c.c. per minute occurred; a change to normal blood brought the flow back again to 8 c.c. The nitrite caused the colour of the lung to change to a chocolate brown. I have repeated the experiment several times, with varied conditions as regards pressure, etc., but always with a similar result, and I think there can be no doubt that sodium nitrite influences the vessels of the lung like the other vessels of the body. Similar dilatation was produced in other experiments by introducing nitrite of amyl into the trachea. (Fig. 135). In all cases a second perfusion of the nitrite again increased the flow.

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[1] *Pflüger's Archiv.*, vol. ix., p. 478.

If, as we have every reason to suppose from these experiments, the administration of nitrites is followed by temporary dilatation of the vessels of the lung, the work of the right heart may be relieved by them, and it seems to me quite possible that some of the good results observed from nitrites in dyspnœic attacks may be the direct result of the relief thus given to the smaller circulation.

DIGESTIVE ORGANS.

The effect of nitrites on the digestive organs varies greatly in different individuals, usually after the ingestion of sodium or ethyl nitrite slight eructations of nitrous gas occur. To some, nitrites act as powerful gastric irritants, the smallest quantity causing sickness and diarrhœa. It is easy to understand the cause of stomach irritation when nitrites are taken by the mouth, for nitrous acid is always at once set free, and to some it acts as an irritant, though most people tolerate it in small quantities, and feel no discomfort from its temporary presence. Where even inhalation causes stomach irritation and diarrhœa it is probably due to excretion of nitrites by the gastro-intestinal tract.

URINARY ORGANS.

From the dilatation of the kidney vessels which nitrites cause we should naturally expect that increase in urinary secretions would follow their use, and doubtless such increase does at times occur. Murrell has seen, after the administration of nitro-glycerine (which acts like a nitrite) to a patient with epispadias, an immediate increase in the flow from the ureter, and nitrous ether has long had the repute of being a diuretic; nevertheless, neither in animals nor men can it be shown that any of the nitrites continuously or greatly influence the urine flow.

In some careful experiments made on animals Atkinson found that small doses of nitrite of sodium either do not affect the urine at all, or sometimes slightly diminish, sometimes slightly increase it, but large doses always decrease it. The urea and uric acid secretion were practically unaffected. In a series of cases I have tried to ascertain the influence of continuous doses of the nitrite of sodium on the kidneys in man.

In twelve non-febrile cases free from cardiac and kidney disease I noted the influence of 3 grains of sodium nitrite given three times daily on the excretion of water during one week, and compared it with the amount excreted in the week immediately preceding and the week immediately following the exhibition of the nitrite. Seven passed more when the nitrite was given, five rather less. In only one was the increase very distinct; here it amounted to 9 ounces per diem, and, as in the week following the nitrites the increased flow was in part maintained, it is not quite certain whether the nitrites were altogether responsible for it. In a second case there was a distinct but not very great augmentation, averaging 5 ounces daily, which was not maintained when the nitrites were stopped. In all the other cases the difference between the quantity passed before and during the administration of the nitrite was too slight to suggest that any influence was exercised by it. In three cases the amount passed the day following the nitrite was distinctly increased. In these two, and a third perhaps where the increase was distinct though less marked, it is probable a temporary effect was produced by nitrites, and I believe that under some conditions nitrites do increase for a short time the secretion of water.

The estimation of urea is open to many fallacies, unless every circumstance is taken into account. I have determined the amount in many cases, and compared the amount passed whilst nitrites were being taken with the amount passed before and afterwards, and the general result I have arrived at is that nitrites do not increase the excretion of urea.

A drug which in a state of health has but little influence on the urine flow may prove a diuretic in certain conditions of disease, but I have been unable to satisfy myself that nitrite of sodium or ethyl can be relied on to act on the kidneys in the ailments for which diuretics are needed.

In some forms of chronic Bright's disease I have seen a considerable increase in the urine follow the administration of sodium nitrite and nitro-glycerine, yet it has never been prolonged. In cardiac dropsy I have not seen continuous diuresis produced.

Notwithstanding that I hold the nitrites in light esteem as diuretics, it is quite likely that a full dose of spirit of nitrous ether has at times a distinct effect in causing a temporary increased urine flow. Half an ounce of spirit of nitrous ether represents, perhaps, the same quantity of rectified spirit and a fair dose of ethyl nitrite. Such a compound is well adapted to act both on skin and kidneys. But I have great doubt whether the administration of spirit of nitrous ether in doses of 15 to 20 minims three times daily as a mixture can be of any service as a diuretic. Even at first the amount of nitrite present is probably too small to influence the circulation sufficiently, and the dissipation of the ethyl nitrite commences as soon as the mixture is made up. One advantage the nitrites certainly have—they do not irritate the kidney.

In the lower animals they have been found capable of producing glycosuria when inhaled or injected, and even in man such an effect is not unknown. Dr. Maragliano,[1] who caused his patients to inhale forty drops of amyl nitrite for forty minutes four to six times daily for the cure of epilepsy, says he found sugar in the urine in most cases.

[1] *Note di Clinica Medica*, Genova, 1880.

TEMPERATURE.

The influence of nitrites on temperature is not an important consideration in their therapeutic use. The quantity in which they are given medicinally is not likely to affect tissue change, but dilating the vessels as they do they at first slightly raise the external temperature. As they expose more blood to the surface they will tend subsequently to lower the body temperature, but the effect in either direction is inconsiderable unless toxic doses are given, which very greatly reduce temperature, perhaps by diminishing oxidation.

PERSPIRATION.

For several centuries spirit of nitre has been a popular diaphoretic, and of its effects and influence in causing perspiration under some conditions there can be no doubt. After drachm doses of 2½ per cent. solution of ethyl nitrite in alcohol I have not infrequently seen in ten to twenty minutes the face bedewed with moisture. In this condition general perspiration has been readily brought on by the application of warmth. The same result has often followed 2 grains of sodium nitrite; in one subject perspiration usually occurred after small doses of any nitrite, even though he was not in bed. As a rule, however, no perspiration is produced by ethyl or sodium nitrites unless in conditions favourable for its occurrence. The diaphoresis is doubtless due to the dilatation of the cutaneous vessels which the nitrites cause, and is therefore but a passing effect. The value of the time-honoured cup of hot gruel, followed by half an ounce of spirit of nitrous ether, it is easy to understand; diaphoresis may result, but the diaphoretic value of 10 to 20 minims of spirit of nitre as usually given medicinally is very problematical.

SUMMARY OF INFLUENCE ON TISSUES.

The chief pharmacological characteristic of the nitrites is their power of temporarily affecting muscle tissue. Under ordinary conditions the amount of nitrite present in the tissues of the living body is not sufficient to disturb the functions of voluntary muscles. But the involuntary muscles and heart are affected by marvellously small quantities of the nitrites; whilst, however, their contractile power is impaired by these small amounts, they are not really injured, for on removal or destruction of the nitrite molecules they rapidly resume their normal function, and no trace is left of the effects of the drug. If frequently exposed to these same molecules they seem to become less readily affected by them.

The tissues of the nervous centres seem to be less easily affected than the muscle tissue, but probably the influence of nitrites is here equally fleeting. Considering the very powerful action of nitrites on muscle tissue, their effects on other structures is very slight. In dilute solutions nitrite of sodium is not a tissue irritant, and is not very destructive to the lower forms of life. Solutions of 2 per cent. and upwards applied to mucous or raw surfaces or injected under the skin give rise to pain, but the same effect is produced by chloride of sodium solutions of the same strength.

CHAPTER IV.

THE NITRATE GROUP.

I PASS on to the pharmacology of the nitrate group before dealing with the therapeutics of the nitrites, because the organic nitrates, about which I shall have most to say, have in some respects a similar physiological action to the nitrites, and it will be convenient to deal with their therapeutic uses together. The similarity seems to arise from the fact that under certain conditions the NO_3 molecule of organic nitrates is reduced to NO_2, and not from any likeness in the action of the two molecules. I do not propose to do more than indicate a few points of special interest in connection with the metallic nitrates.

I have already pointed out the very marked difference in toxic influence on skeletal muscle between the groups NO_2 and NO_3, when combined with a metal of small physiological activity like sodium. I have shown that whilst nitrite of sodium is a powerful muscle poison, the nitrate tends to preserve muscle vitality. The striking contrast between the action of these two salts can only depend on the difference between the physiological properties of the groups NO_2 and NO_3. This difference can be traced in all the metallic compounds of the two groups.

The nitroxyl ONO gives evidence of its influence in every compound into which it enters. The nitrate group ONO_2 plays a neutral part, and does not seem to interfere with the physiological activity of the metals with which it combines.

I have already shown this with regard to the sodium salts, and have only to add that in dilute solutions of the nitrates of potassium, barium, calcium, and strontium, the physiological influence of these metals on the skeletal muscles is as well seen as in the corresponding chlorides.

Dilute solutions of nitrate of sodium are as little irritating to the mucous membranes and raw surfaces as they are to muscular tissue. It is commonly thought that the nitrates of potash and soda are irritants; as a fact, however, their solutions when dilute are not more irritating than a solution of sodium chloride of corresponding strength, and their presence in water, up to a certain amount, prevents the irritation of mucous membranes which water itself causes.

A solution containing under 2 per cent. of either chloride or nitrate coming into contact with the Schneiderian membrane, the conjunctiva, or raw surfaces gives very little discomfort; if, however, left long in contact with a raw surface it gives rise to severe pain, and a stronger solution of either salt is at once painful.

By the stomach mucous membrane a 10 per cent. solution of sodium nitrate is well borne, but if more concentrated and in considerable quantity, it may cause great irritation like other strong saline solutions.

The organic nitrates to which I shall allude are glyceryl trinitrate, $C_3H_5(ONO_2)_3$ (nitro-glycerine); ethyl nitrate, $C_2H_5ONO_2$; propyl nitrate, $C_3H_7ONO_2$; isobutyl nitrate, $C_4H_9ONO_2$; isoamyl nitrate, $C_5H_{11}ONO_2$. In these organic nitrates two effects have to be considered: (1) the actions of the compounds themselves; (2) that resulting from the products of their decomposition.

NITRO-GLYCERINE.

I shall speak of nitro-glycerine first, because of its great therapeutic importance. Professor Hay has shown that nitro-glycerine, in the presence of alkalies and their carbonates or of sodium phosphate, is decomposed, about two-thirds of the ONO_2 being reduced to ONO and uniting with the alkali to form a nitrite; the remaining third forms a nitrate with the alkali. It is even decomposed under some conditions by contact with water.

When nitro-glycerine is taken into the stomach it probably undergoes little or no change there, but is absorbed unaltered and quickly converted in part or altogether into sodium nitrite. Any part which is not thus destroyed is excreted by the kidneys, and when large doses are given to animals by the mouth nitro-glycerine has been recovered from the urine and the blood. After large medicinal doses in man it has been detected in the urine. On the skeletal muscles, the vessels and the excised frog's heart, dilute solutions of nitro-glycerine act exactly like solutions of sodium nitrite of similar strength. The gastrocnemius of a frog in normal saline containing 1 part in 1,000 of 1 per cent. solution of nitro-glycerine dies in 20 to 40 minutes, as it would do in the same strength of sodium nitrite, and it gives when contracted a similar muscle tracing. The dilatation of the vessels of the tortoise when weak solution of nitro-glycerine is perfused through them, is just as great as with sodium nitrite. (Fig. 136). Inasmuch as nitro-glycerine is decomposed to some extent in the experiments, nitrite being formed, it is impossible to say how far the effects are due to the nitro-glycerine itself.

When given internally the effects of nitro-glycerine are almost identical with those of sodium nitrite, but in a few points the action of the two substances differs somewhat. Nitro - glycerine tends to stimulate the spinal cord and medulla, and in the lower animals, especially the frog, may cause tetanic spasms. Sodium nitrite has no such effect.

In man the only difference observed, so far as regards the nervous system, between nitro-glycerine and sodium nitrite is that the former much more often causes headache, which, when induced, is at times of longer duration than that caused by sodium nitrite.

The throbbing headache felt immediately after nitro-glycerine may be due to the direct effect on the circulation of the nitrite into which the trinitrate of glyceryl is converted. But it at times lasts many hours after the circulatory effects have apparently passed away, and it seems possible that the nitro-glycerine headache is not entirely due to the nitrite effect, but that the nitro-glycerine molecule, or it may be certain compounds, due to decomposition of the glyceryl, take some part in its production. There can be little doubt that the tetanus produced in the lower animals is due to the nitro-glycerine molecule itself.

The difference between the effects produced on the circulation in man between sodium nitrite and nitro-glycerine, though small, are yet of some practical importance. From the table (page 100) it will be seen that the action of nitro-glycerine is more rapid than that of sodium nitrite or ethyl nitrite.

Not only is the action of nitro-glycerine distinctly evident earlier than that of the nitrites of sodium and ethyl, but the point of the lowest pulse tension is also earlier, as seen in the table which I have given. I have not, however, found the influence of a minim of nitro-glycerine solution usually quite as prolonged as the influence of 2 grains of nitrite of sodium (Fig. 130), but there is no important difference. The minute amount of nitro-glycerine which will affect the pulse is very marvellous. One-sixteenth of a minim of liquor trinitrini will, in some, distinctly lower tension. The effect of small doses is more remarkable when we consider the very large doses which the circulation will bear without suffering injury. Dr. Murrell records that on one occasion he gave a patient 110 minims eight times daily, the only effect being to relieve anginal pain and cause some headache. I have only to add the explanation which Hay has given of the more powerful influence of nitro-glycerine than nitrite of sodium. The glycerine compound is absorbed into the blood and then forms a nitrite. The sodium nitrite undergoes decomposition by the acids of the stomach, and though the nitrous acid set free is in part absorbed, there is naturally considerable loss by escape of the acid vapour and by its decomposition.

THE FATTY NITRATES.

The nitrates of ethyl, propyl, butyl, and amyl are all stable bodies very slightly soluble in water and not disagreeable to smell or taste. The boiling point of the series increases with the molecular weight, nitrate of ethyl boiling at 190° and nitrate of isoamyl at 296°.

Unlike nitro-glycerine, the nitrates of ethyl, propyl, butyl and amyl do not readily decompose even when mixed with an alkaline fluid. When I added 0·2 c.c. of these nitrates to 10 c.c. of a 5 per cent. solution of sodium carbonate, and kept the mixture at 38°C. no trace of nitrite could be detected in 30 minutes. On leaving the mixture for several hours the tests indicated the presence of a trace of nitrite, but it was not till 6 days had elapsed that any considerable quantity of nitrite was present. On adding 2 per cent. of ethyl nitrate to blood, methæmoglobin does not immediately appear, but on keeping the mixture at 38° C. the characteristic band can be detected by the spectroscope in about 30 to 40 minutes. The nitrates of the higher members of the series isobutyl and amyl do not under similar conditions show the presence of methæmoglobin for many hours. I have several times dialysed the mixture of nitrates and blood in which methæmoglobin has been produced without detecting the presence of nitrites in the dialysate, though on keeping the compound for 24 to 36 hours at 38° a nitrite reaction is obtained from it; manifestly, however, the fatty nitrates do not yield nitrites as easily as nitro-glycerine does.

Although the nitrates seem to be decomposed into nitrites with some little difficulty outside the body, it seems probable that in the living body the change takes place more readily, since, as I shall show, an effect on the circulation somewhat like that caused by nitrites is produced by giving the nitrates, but this nitrite effect is less quickly produced and longer lasting than when nitro-glycerine is given.

When a muscle is exposed to a mixture of 1 of ethyl nitrate in 1,000 of normal saline solution the contractions diminish in height somewhat more rapidly than with normal saline, but vitality is well maintained and the muscle lives as long as in normal saline. (Fig. 137). 1 in 500 causes a somewhat rapid fall in the height of the muscular contractions, but a muscle will live in the solution over three hours.

Propyl nitrate diminishes the irritability of muscle more powerfully than ethyl nitrate, but the muscle will continue to live in a solution of 1 in 1,000 of normal saline, and give contractions at the end of 24 hours.

Isobutyl nitrate, of the strength of 1 in 1,000, greatly decreases the contractile power of muscle. At the end of about three hours it will only contract as a rule with strong stimulation.

Amyl nitrate is far more fatal than any of the other nitrates. If the muscle is immersed in 1 of 1,000 of amyl nitrate the contractions rapidly fall and the muscle dies in about an hour, contracture being often seen. The relative influence of nitrates as shown by their action on muscle bears out the well known fact that the toxicity of alcoholic radicles increases with their atomic weight.

The effect of the fatty nitrates on the vessel walls does not quite run parallel with their effect on skeletal muscles. Ethyl nitrate in the strength of 1 in 1,000 dilates the vessels, as shown in a perfusion experiment with a tortoise.

Ethyl nitrate increased the flow through the vessels of a tortoise by 50 per cent., but propyl nitrate in the same amount still more powerfully dilates the vessels, and if a solution of 1 in 5,000 be used extraordinary dilatation takes place. (Fig. 142).

I shall point out when I come to speak of nitro substances that with them, too, the propyl compound seems to possess the strongest dilating power.

Isobutyl nitrate, in the strength of 1 in 1,000 of normal saline contracts the vessels. But in a strength of 1 in 5,000 to 1 in 10,000 it dilates them very distinctly.

Isoamyl nitrate very markedly contracts the vessels in a strength of 1 in 1,000 of normal saline, the flow through them being very greatly decreased. (Fig. 143). Dilute solutions, even 1 in 10,000, do not dilate the vessels, but very weak solutions, 1 in 30,000, have a slight dilating effect.

It is interesting to notice the rise and fall of the dilating influence due apparently to the alcoholic radicles.

Nitrate of ethyl renders the action of the isolated frog's heart slightly quicker and weaker when in the strength of 1 in 1,000. (Fig. 138). The other nitrates have much the same effect as the ethyl compound, but are more toxic.

The chief interest in the action of the nitrates centres on the powerful and long-lasting influence they exert on the circulation in man. If 5 minims of ethyl nitrate be taken internally the pulse tension falls in three or four minutes, but usually not very considerably. It continues to fall, and reaches its lowest point in thirty to sixty minutes; sometimes it is very low for a longer time than this. The effects of ethyl nitrate on the pulse can often be distinctly seen four or five hours after a dose has been taken. (See Fig. 139).

As after nitrites, the pulse is somewhat quickened, but this effect is by no means marked. One minim has a distinct effect on the pulse. Propyl (Fig. 140), isobutyl (Fig. 141), and amyl nitrates (Fig. 133) all act in a similar manner, and as far as I have examined their action, they depress the tension for a longer time than the corresponding nitrites. Fig. 141 shows the effects of isobutyl nitrate on the man from whom the tracings after amyl nitrite and nitrate were taken.

The inhalation of the nitrates very slightly lowers tension. The long-lasting action of the nitrates is doubtless due to the fact that, unlike nitro-glycerine, they are somewhat difficult of decomposition. I have found the nitrate of ethyl useful in various ailments for which nitrites are usually given. There is one drawback to its use. It seems to cause a headache more often than ethyl nitrite; this headache does not always come on immediately the drug is taken; it may not appear for four or five hours. The other nitrates also tend to cause more headache than the corresponding nitrites.

CHAPTER V.

THERAPEUTIC USES OF THE NITRITES AND NITRATES.

IN considering the bearing of the pharmacological action of the nitrites on their therapeutic application there are three points worthy of note. The first is the minute quantities which may influence the vascular system, and, as a consequence, certain functions of the body. An eighth of a grain of sodium nitrite, a small but uncertain fraction of a minim of ethyl nitrite, or one sixteen-hundredth of a grain of nitro-glycerine will in many distinctly affect the circulation.

A second point is that, notwithstanding their potency, even large quantities of the nitrites and nitro-glycerine do not readily cause death. Although unpleasant and even alarming results have been known to follow comparatively small doses, there has been, as far as I know, only one case recorded in which a fatal result has been attributed to their medicinal use. This is the more worthy of notice since these drugs have been commonly given in serious cases. I do not know of an instance in which ethyl nitrite or sodium nitrite have proved fatal, though very large doses of the latter have been administered. Amyl nitrite has been swallowed by the dessertspoonful, yet recovery has, I believe, always occurred, and severe though the symptoms are which follow its inhalation no harm has ever accrued from its employment, save in one instance, a case of phthisis, where death followed the inhalation of 7 drachms. Considerable quantities of nitro-glycerine have been taken with impunity, so far at least as concerns a fatal result; only in few instances have very large amounts, taken accidentally or for suicidal purposes, caused death.

A third point which it is important to bear in mind is the evanescence of nitrite action. When nitrites advantageously alter functions their direct influence for good usually soon ceases; on the other hand, their evil effects are also short lived; there is no cumulative influence.

ANGINA PECTORIS.

The pharmacology of the nitrites and nitro-glycerine indicates the class of cases in which these drugs will be of the most utility—namely, those in which the heart is embarrassed in its work owing to a want of due relationship between its power and the calibre of the vessels through which it transmits blood.

Angina pectoris is the most conspicuous ailment of this class. It would be out of place here for me to discuss its pathology and its various forms, but there are one or two points to which I must allude, because they are intimately connected with the use of nitrites. Angina pectoris has been defined by Sir Richard Quain as "an affection of the chest accompanied by severe pain, faintness, and anxiety, occurring in paroxysms connected with disorders of the pneumo-gastric and sympathetic nerves and their branches, and frequently associated with organic disease of the heart."

It is manifest that for the production of angina as thus defined, a variety of pathological conditions may suffice. Alterations in the cardiac nerves and plexuses due to intrinsic structural changes, or to their involvement in diseased conditions of adjacent organs, may lead to periodic neuralgic attacks similar to those which we see in other parts of the body when nerves or plexuses are similarly affected. Neuralgic pains referred to the heart may be the outcome of reflected irritation originating elsewhere, as, for example, in the abdominal organs. Hysterical pains may be felt in the cardiac region as well as in other parts. All these causes may perhaps lead to paroxysmal pain apart, or almost so, from circulatory changes connected with alteration in tension. But clinical observations do, I think, indicate that a large proportion of anginal attacks are directly caused by a rise in tension, and there seem to me good grounds for believing that this rise is due to a temporarily decreased calibre of the systemic or pulmonary vessels, and a consequent suddenly increased call on the propelling action of a heart the walls of which are more or less altered in structure.

In some cases, as Dr. Douglas Powell has so well pointed out,[1] the call may be made upon a diseased heart (angina pectoris gravior); in others there is more or less cardiac reserve power and integrity (angina pectoris vaso-motoria); but in both forms the symptoms are due to the fact that the heart is unequal to the work it is called on to perform.

With a view of removing the high tension ensuing from this contraction, Dr. Brunton first made trial of amyl nitrite in angina pectoris, and discovered its wonderful power of relieving the cramp-like pain which accompanies this ailment. Of late, however, doubts have been raised as to whether high tension is really the cause of pain; and it has been suggested that nitrites relieve, not because they lower tension, but because they act as analgesics, and remove the pain which causes high tension. It seems to me that for this theory there is but little foundation; experiments, as I have said, give no indication that nitrites are direct analgesics; in poisonous doses, indeed, they depress the functions of all portions of the nervous system, but the afferent portion is the last which is affected. So powerful an analgesic as morphine not infrequently fails to relieve the pain which a minute dose of amyl nitrite at once removes, and there is, I hold, no warrant for the assumption that nitrites or nitro-glycerine have a special analgesic influence on the cardiac plexus. I cannot see sufficient ground in what has so far been advanced, for calling in question the opinion that increased tension is the cause of suffering in a large proportion of cases in which paroxysmal pain is referred to the heart; and that in the treatment of angina pectoris it is important, in the first place, to lower this tension as speedily and efficaciously as possible.

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[1] *Practitioner*, vol. xlvi., p. 255.

In the reduction of tension by nitrites we have three objects in view: (1) to relieve pain as rapidly as possible; (2) to avert a fatal termination; (3) to prevent the recurrence of pain. The second object is for the time attained when the pain is removed.

The pain of angina varies greatly in duration; generally it is short in the earlier stages of the disease and abates quickly when the immediate cause, usually some movement, has ceased. Not infrequently, especially towards the termination of a long-standing case, atrocious pain is present for many minutes, sometimes for many hours. But, whether the duration of pain be short or long, those nitrites are manifestly, in the first instance, called for which act most quickly.

What I have stated with regard to the time at which the influence of the various nitrites on the circulation is first distinctly perceptible, points clearly to the drugs which may most advantageously be used during anginal pain. It has been shown that propyl, isobutyl, and amyl nitrites reduce the tension in a few seconds, whilst sodium nitrite takes from two to five minutes to act, and ethyl nitrite about the same time. Even nitro-glycerine, which affects the circulation in from forty seconds to two minutes, acts much less rapidly than do the fatty nitrites when they are inhaled.

Manifestly then to relieve urgent pain and its concomitant danger, the fatty nitrites should be inhaled. Hitherto an impure nitrite has been chiefly used for this purpose. The nitrite of amyl of the British Pharmacopœia is a mixture of many nitrites, and contains likewise amyl alcohol, and oxidation products such as valeric aldehyde, valeric acid, and amyl valerate. Dunstan and Woolley, in one specimen found less than 40 per cent. of the amyl nitrite, and in another 50 per cent., but in addition 10 per cent. of isobutyl nitrite.[1]

Even the impure amyl nitrite now used is a most valuable drug, but considering the importance of the influence required, it seems desirable that a more definite compound should, if possible be introduced. Of late isobutyl nitrite has been employed occasionally as a substitute for amyl nitrite. Cash finds isobutyl and secondary propyl nitrites somewhat more active in reducing tension than the amyl compound. It has appeared to me, too, that isobutyl nitrite more certainly relieves anginal pain than does the official amyl nitrite.

The inhalation of amyl nitrite sometimes fails to relieve the pain of angina pectoris; this failure may arise from several causes:—

(1) The paroxysms may be due to neuralgia of local origin, or it may be reflected or hysterical, and circulatory changes may take but little part in its production. In such conditions nitrite inhalations can do no harm, yet they may fail to relieve pain.

(2) In some cases the nitrite does not remove pain because of the short duration of its action. It does not break the spell of the vessel contraction. There may be relief, but it is not complete, and when in a minute or two the effect of the drug passes off, the wave of contraction returns, and with it the pain.

(3) Some are curiously insusceptible to the influence of amyl nitrite. In such people full inhalations may succeed when slight ones fail, though this is not very common. If a certain measure of success is not obtained with ordinary inhalation, it is not often that a more copious use of amyl nitrite completely removes anginal pain.

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[1] *Pharm. Journ.*, 1888, p. 489.

(4) Lastly, in very advanced cases where the attacks of pain continue long, amyl nitrite may entirely fail to relieve the pain, though in an earlier stage it proved useful for this purpose.

If from any of these causes amyl nitrite does not remove pain, one of the nitrites whose effects are more persistent should be tried. Of the official preparations, nitroglycerine is by far the best. On referring to the table it will be seen that it reduces tension more quickly than sodium nitrite, more quickly, too, than ethyl nitrite. Beginning with one drop of liquor trinitrini, the dose may be gradually increased until either the pain is relieved or unpleasant physiological effects as throbbing in the head or palpitation show that no more can be borne. In pain of hysterical or reflected origin this physiological limit is often quickly reached; in other cases very large doses may be given before relief is obtained.

Dr. Murrell, to whom we owe the introduction of nitroglycerine as a remedy for angina pectoris, has given, as I have said, 110 minims eight times daily. Some are very insusceptible to nitrites, especially when passing through a dyspnœic attack, and it is worthy of note that the same individual may be more susceptible at one time than another.

A patient, L., from whom several of the tracings I show have been taken, came into the infirmary with intense dyspnœa and cyanosis, and some cardiac dilatation. The nitrites of amyl and ethyl seemed to have no effect in relieving the dyspnœa, and the ordinary effect of the amyl compound he did not feel. Nothing was of service except free venesection, which at once relieved him. The next day even, his pulse was somewhat refractory to nitrites, ordinary doses of sodium and amyl nitrites only affecting his circulation slightly. The pulse tracing, taken a month later, showed that he was then fairly susceptible to 2 grains of sodium nitrite; then he commenced to take the nitrites regularly, and in another month I found the tension of his pulse but little influenced by this dose, though by stronger doses it was readily brought down. As I have before said, people with high tension are less affected by nitrites than those with low tension. I have several times had occasion to gradually raise the dose of liquor trinitrini to 20 minims; it not infrequently happens that larger doses are required as a case progresses, and I believe it is far safer to employ somewhat large doses of nitro-glycerine than to resort to morphine injections, which in the later stage of angina pectoris generally fail to give relief, and I suspect, at times, hasten the fatal termination. Let me say here that I look on the injections of morphine in severe paroxysmal cardiac pain as by no means devoid of danger. It is quite true that they often give relief in anginal attacks, and are not usually followed by dangerous symptoms, but I have myself twice seen death occur shortly after subcutaneous injection of morphine in a prolonged anginal attack, and in the experience of others I find a fatal termination so frequently a sequence of an injection of morphine that it savours strongly of cause and effect. From the use of nitrites I can find no evidence that fatal results appear to follow, notwithstanding the large doses in which they have been given, and the critical condition of many of the patients who have taken them. On the other hand, I have several times seen reason for believing that life has been shortened owing to the want of nitrites or their use in too niggardly a fashion, and on more than one occasion it has seemed as if the immediate cause of death has been an unreplenished nitrite bottle.

Every person who suffers from angina pectoris, and who has derived relief from nitrites, should have immediately at hand amyl nitrite, or the tabellæ or liquor trinitrini.

To prevent the recurrence of anginal attacks amyl nitrite is, of course, of no service, but nitro-glycerine is as useful in preventing attacks as in relieving them. A sufficient dose should be given a few minutes before an exertion which is likely to cause an attack of pain. The amount which is sufficient can only be determined by the effect on the patient; sometimes one drop will suffice to ward off attacks for two or three hours; oftener larger doses are required. One patient, for example, finds not less than twenty-five drops necessary in order to enable him to perform light work for some hours, and for six months has, by the aid of this dose once or twice daily, been enabled to live and earn a livelihood in fair comfort. Danger, I believe arises not from the size of the dose or from its frequent repetition, but from too great fear of the drug.

To those in whom the anginal pains are connected with serious cardiac degeneration the time at length arrives when severe cardiac pain, which may be long continued, comes on without apparent cause; the end is then usually near at hand. Here the frequent use of large doses of liquor trinitrini will not suffice either to prevent or ward off all pain, but it is the most effective means we possess, and if it does not prevent suffering, it at least mitigates it without adding to danger. Nitro-glycerine is so quickly absorbed in the stomach that subcutaneous injection is, as a rule, not necessary; but in cases of urgency, where there is fear that the absorptive power of the stomach is in abeyance, it may be resorted to. At times nitro-glycerine is not well borne, owing to the headache which it causes; sodium or ethyl nitrite may then be tried, especially for the purpose of preventing paroxysms. The sodium compound may be used, beginning with 2-grain doses, but I do not think it usually agrees so well with patients as nitro-glycerine when large doses are required. A 2½ per cent. solution of ethyl nitrite in absolute alcohol I have often used, giving doses of one or two teaspoonfuls. The solution should be mixed with water immediately before being taken, otherwise the nitrite rapidly escapes.

Of late I have employed the ethyl nitrate, which has distinctly a longer lasting influence in reducing tension than the nitrite, and in some ten or twelve cases in which I have used it the testimony in favour of its prolonged beneficial action has been satisfactory. A medical man, who has been under my care for angina pectoris, has at my request compared on himself the effects of various nitrites, and places the nitrate of ethyl distinctly above the nitrites in the length of time it wards off the attacks. In another case a woman, aged 28, who had suffered from anginal attacks for three or four months, and who found relief during the attacks both from nitro-glycerine and the inhalation of amyl-nitrite, I found nitrate of ethyl give more continuous relief than nitro-glycerine. For two or three days she took 3-minim doses of the ethyl nitrate at intervals of three or four hours; in this quantity the attacks, though not prevented, were lessened in frequency. As the heart's action seemed quickened, she returned to the occasional use of the nitro-glycerine, but soon afterwards the attacks became more frequent and less amenable to relief by this drug. One morning, in the absence of one of my colleagues, I saw her, and found her with severe cardiac pain, which had lasted an hour, and which nitrite of amyl and nitro-glycerine in small doses had failed to relieve. A drachm of a 10 per cent. solution of nitrate of ethyl, the last I happened to have at the time, was then given to her. In ten minutes the tension was lowered as shown by the tracing, and the pain entirely disappeared.

A few hours later it recurred. Nitro-glycerine gave slight relief, but only for a very short time; nitrite of amyl failed entirely to remove the pain. A subcutaneous injection of morphine guarded by atropine was now cautiously given, only two doses of the eighth of a grain being injected with an interval of half an hour. Hardly the slightest relief followed; the pain continued for three hours. Then she became cyanotic, and died somewhat suddenly. At the *post-mortem* examination the aortic valves were insufficient; one of the coronary arteries was found small, and the other almost obliterated. My experience of the use of nitrate of ethyl in angina pectoris and other ailments is not sufficiently large to enable me to form a definite opinion as to its value as compared with nitrites, but the long period during which it lowers tension in healthy subjects, and its very definite effects in the few cases of angina in which I have tried it, lead me to think it may prove of value. The nitrate of propyl, isobutyl, and isoamyl are as effective in lowering tension as nitrate of ethyl, but the tendency to cause headache—which is, I think, even more marked with the nitrate than the nitrite of ethyl—is a still more prominent feature in the action of the propyl, isobutyl, and isoamyl compounds, and I have not used them medicinally.

Although I regard the nitrites and the organic nitrates as of the greatest value in relieving and preventing anginal attacks, and in helping to ward off the fatal result in which any attack might terminate, I cannot rank them high as curative agents.

Doubtless, when attacks of angina are warded off and rendered less severe by the use of tension depressors, recovery does at times take place, as Dr. Murrell has well shown in some of the cases which he has so graphically described in his book on *Nitro-glycerine*. The relief from pain and suffering may tend to prolong life, and when regularly given the heart's work may be so decreased that its nutrition may improve. Perhaps, too, the vessel walls gain some advantage from the fact that under the influence of the nitrites their continued contest with the blood current is somewhat lessened. But I am by no means satisfied that the recoveries from angina pectoris which have been reported after nitrites and nitro-glycerine are really due to these drugs. Their employment is only one element, though an important one, in the treatment of angina. It should be accompanied by the use of those agents calculated permanently to improve the condition of the vascular system, among which I believe iodide of potassium and arsenic hold a foremost place.

CARDIAC DYSPNŒA.

Next to the relief of angina the nitrites are of most service in the prevention of dyspnœa connected with other forms of cardiac and with pulmonary disease. The theories which have been broached to account for cardiac dyspnœa are many in number, but hyperdistension of the pulmonary vessels is regarded in most cases as the immediate cause of the continued shortness of breath associated with cardiac dilatation and valvular lesions. The heart is at times unable to send the blood on its way through the system, because, owing to the weakening of its walls or the narrowing of the vessels, there is a disproportion between the power of the heart and the obstacle it has to overcome; from these causes or from a defective valve the pulmonary vessels may be kept constantly overfull.

The dyspnœal paroxysms may depend immediately on many causes, but most frequently they are due to sudden increase in the difficulty which the heart experiences in driving the blood onwards through the systemic system, either from a passing increased narrowness of the arterioles or from a temporary failure of cardiac power. Paroxysms of dyspnœa in cardiac disease may likewise occur from exacerbations of pulmonary hyperæmia and œdema. Unfortunately it is not always possible to determine whether attacks of dyspnœa with which we have to deal are due to heart failure, vascular contraction, or some other cause: often, indeed, more causes than one are present, hence the difficulty of coming to any conclusions as to the cases in which tension reducers may be of service, but in certain forms of cardiac trouble they are usually of special value.

In the dyspnœic attacks which so often accompany cardiac dilatation connected with alcohol, gout, etc., I have seen nitrites of ethyl and sodium and nitro-glycerine give much relief. By dilating the vessels for a time they enable the heart to do its work, and thus relieve the congestion of the lung vessels. The question arises: If the dyspnœic attacks are connected with cardiac failure, can they do harm in virtue of their cardiac depressant influence? I believe large doses might work evil, but in small quantities, such as 1 to 2 drops of 1 per cent. nitro-glycerine, 1 to 2 drachms of the $2\frac{1}{2}$ per cent. solution of nitrite of ethyl, or 2 grains of sodium nitrite, the action is always in favour of the heart. These small quantities can powerfully dilate the vessels, but they do not, in an important measure, depress the heart. Experiments on animals, as I have pointed out, show that very small quantities increase rather than decrease the amount of work a heart can do. I have given the doses I have named in a very large number of cases, and never seen the slightest indication pointing to possible evils. The amount administered may be cautiously increased without any risk if the relief be insufficient, or the efficacy first noticed seems afterwards to fail.

In the case of nitrites, increase of danger is not proportioned to increase of dose. When relief is not obtained by a small dose, and when no physiological effects follow, such as throbbing in the head or palpitation, I find it quite safe to repeat the dose in half an hour. It is desirable, when the larger doses are given, or when the drug is given more frequently, that the patient should rest. Discomforts which have arisen after small doses of the nitrite, such as 3 grains of sodium nitrite, have for the most part occurred in those who have been pursuing their ordinary avocations.

I am not deterred from giving nitrites in dyspnœa by irregularity or weakness of the pulse, for I find that in dyspnœa they do not tend to cause syncope or lead to heart failure. Dr. Sansom has published a case in which a patient with an extremely weak and irregular heart's action was in the habit of taking six to twelve nitro-glycerine tablets daily without medical advice. I have met with one or two similar instances in which people with very dilated hearts have found such relief from nitro-glycerine tablets that they have continued to take them for months, and I have no doubt that many sufferers take them habitually without advice. I can easily conceive that grave mischief might arise, but, so far, I have met with no record of it. Fortunately, there seems to be a special tolerance of nitrites in such cases. When with cardiac dilatation moist sounds at the base give evidence of bronchitis or lung œdema, the nitrites generally fail to relieve but by no means always. Partial relief is indeed not uncommon, and a few doses of a nitrite are always worthy of trial.

In the paroxysms of dyspnœa which occur in many valvular diseases of the heart the nitrites are sometimes of great service. But here, as in simple cardiac dilatation, they often fail when there are abundant moist sounds at the bases of the lungs. They will fail to remove dyspnœa, too, as all other remedial agents fail, in very advanced conditions of cardiac disease, yet even in the most unpromising cases they are at times of the greatest value in the relief of distress, so much so that patients will often beg for the repetition of the dose which has given so much comfort.

The nitrites are naturally most useful in mitral disease, since here paroxysmal dyspnœa is more frequent than in aortic troubles, but aortic incompetence is no bar to the use of nitrites in small quantities when the breathing is oppressed. In valvular disease as in simple dilatation, weakness and irregularity of the heart's action need not be taken into account in giving small doses of the nitrites for dyspnœic attacks; such doses do no harm even if they do no good. In a few cases, as I have already said, I have known irregularities cease under their employment.

Against the utility of nitrites in cardiac dyspnœa it might be urged that as their vascular influence is but transitory, so also will be the relief they give, and this is true;

but here, as in the case of other remedies, we find that relief is not limited to the period during which the medicine directly acts. When unduly contracted arteries are dilated, they do not forthwith resume their contracted condition as soon as the effect of the nitrite on the vessel wall has passed away. Whether the dilatation of the pulmonary vessels by nitrites is one factor in the relief they give in cardiac dyspnœa we cannot say, but the very marked effect they can be shown experimentally to produce in dilating these vessels seems to render it likely that, besides increasing the calibre of the systemic vessels and easing the left heart, they at the same time, by widening the lung vessels, relieve the strain on the right heart.

Since paroxysmal cardiac dyspnœa has many causes, some of which are not influenced at all by vascular dilatation, it follows that sometimes no relief is obtained from nitrites, but, as a routine remedy for this dyspnœa, I believe there is nothing better.

For the past two or three years nitrites have been resorted to habitually in my wards of the infirmary at Manchester, in all forms of dyspnœa. Comparing their effects with those obtained from ether and ammonia in paroxysmal attacks of cardiac dyspnœa, I have no hesitation in saying that the nitrites are by far the most beneficial. I have used a solution of nitrite of ethyl in absolute alcohol, but nitro-glycerine or nitrite of sodium with alcohol might be in some respects perhaps better since they are more stable.

For the permanent short-breathedness of cardiac disease the nitrites are, I believe, less useful than for dyspnœic attacks. Occasionally a measure of relief may be given to the heart's work by them which is doubtless beneficial to this organ, but I do not think it possible to keep the tension permanently low, either by nitrites or nitro-glycerine, for by persistent administration at short intervals their vascular dilating power lessens somewhat, and, with large continuous doses, methæmoglobin might be produced. I have found some patients with weak dilated hearts, and suffering from dyspnœa on slight exertion, experience great relief from a few small doses daily of nitro-glycerine, and I think I have seen some permanent advantage derived from this treatment. In some other special conditions connected with cardiac disease the nitrites have been found of service, as, for example, in aortic insufficiency with hypertrophy and severe headache.

We often meet with patients just past the middle period of life, stout, and with some evidence of fatty cardiac change, who feel a sense of discomfort on any exertion, and are therefore unable to take exercise, and who at times have somewhat smart attacks of dyspnœa from slight causes. In these cases I think the nitrites not only useful in the attacks, but also in giving comfort when taken regularly. A tablet or two of nitro-glycerine, when taken twice daily, will often remove long-standing discomforts due to the readiness with which dyspnœa is excited, and a permanent improvement at times ensues, because, with the aid of the nitro-glycerine, patients are able to take a certain amount of exercise.

Even in advanced fatty changes I have no hesitation in giving small doses of the nitrites, both to relieve and prevent dyspnœa. I question whether the heart in this condition is weakened by them at all, but of this I am quite sure, it is much relieved and aided in its work.

Syncope and Cardiac Failure.

A difficult question to decide is whether nitrites should be used in syncope and cardiac failure.

The flushed face produced by amyl nitrite led to the idea that it might be of service in syncope, for which purpose, indeed, it was proposed in the first paper on its action, by Guthrie in 1859. In 1871 Dr. Goodhart again suggested its use in sudden failure of the heart's action, and in the same year Dr. Talfourd Jones gave it with apparent advantage to a patient who had fainted. Since this time it has often been recommended and given in cases of apparent heart failure from various causes, including cardiac failure due to chloroform, and so far as I am aware no evil consequences have ever appeared to result from its employment; on the contrary, distinct and immediate improvement in the patient's condition is said to have followed its use.

Nitro-glycerine, too, has been given in syncope and collapse, and in one case of collapse during the passing of gall stones; and when the patient was pulseless it is recorded that ten drops of a 1 per cent. solution of nitro-glycerine were injected with advantage.

Reichert especially has claimed the nitrites as valuable cardiac stimulants, and in support of his contention has marshalled a series of cases of heart failure, in which they seemed to prove useful. As I have indicated when speaking of the pharmacology of the nitrites, there is ground for thinking that the initial influence of small doses of nitrites on the circulation is a stimulant one, notwithstanding that they are so capable in large doses of weakening the heart's action. Syncope is the result of a failure of the heart to supply the cerebrum with a due amount of blood, and to this failure arterial dilatation and lowered tension sometimes contribute. When this is the case it would appear that the administration of nitrites might be gravely dangerous since they so powerfully lower tension. But spasmodic contraction of the arterial vessels is probably in some cases one cause of the insufficient supply of blood which leads to syncope, and here for increasing the cerebral supply, nitrites would be of service.

When, too, sufficient blood is not driven into the brain, owing to deficient power in the heart itself, nitrites may be useful by their direct influence on this organ, and indirectly by dilating the vessels, and thus relieving the heart of some portion of its work.

Whilst then in some forms of syncope harm might be done, and even a fatal result brought about by full doses of nitrites, it seems very probable that in others good results will follow from their employment, and since no bad effect has yet been recorded from the use of nitrites in syncope, whilst in many cases great advantage has followed their use, the employment of small doses of nitrites in syncopal conditions seems to be well justified.

In cardiac failure, too, there is evidence that good results have followed both from the use of amyl nitrite and nitro-glycerine, and it seems to me that these are grounds for the use of the drugs in small quantities. A failing heart will under their influence beat more quickly, and will be relieved of a certain portion of its work by the dilatation of the vessels. But the difficulty is to graduate the amount of nitrite to the necessities of the heart. If any nitrite were by inhalation thrown into the blood in large quantities, it might stop the action of a failing heart.

PULMONARY DYSPNŒA.

For the relief of dyspnœa due to asthma and bronchitis, the nitrites and nitro-glycerine have been occasionally used since Dr. Talfourd Jones, in 1871, recorded the beneficial effects of the inhalation of amyl nitrite during an asthmatic paroxysm. Five years ago Professor Fraser published the results of his investigations on the influence of the nitrites of amyl, ethyl, and sodium in the dyspnœa connected with asthma and bronchitis[1]. He found that in asthmatic paroxysms the inhalation of these nitrites was capable of completely relieving the respiration, and removing the adventitious lung sounds. Usually the rhonchi returned when the effect of the nitrites passed away; at times the relief was permanent. With the nitrites of ethyl, sodium, and nitro-glycerine, he generally noted in half a minute a decrease of the adventitious sounds, lessened dyspnœa, and relief in three to five minutes. As might be expected, the effects were more prolonged than after nitrite of amyl. In 61 observations made on 25 patients suffering from bronchitis, in some cases accompanied with dyspnœic paroxysms, the nitrite in 48 removed every vestige of rhonchus or sibilus for various periods of time. In 10 the sounds were lessened, but they were not altogether silenced; in three the effects were slight or negative, and in these the dyspnœa was not relieved. I cannot say my experience of the use of nitrites in asthma and bronchitis has been as favourable as that recorded by Fraser. Nevertheless, I have seen a large measure of relief afforded in pulmonary dyspnœa by them. In typical asthma I have often seen complete and rapid relief afforded, yet in some cases hardly the slightest benefit arises either from inhalation of amyl nitrite or from the administration of large doses of the other nitrites. In the less severe asthmatic attacks, which are apt to come on from time to time in nervous people subject to slight bronchitis, the attack is almost always cut short by nitrites; and where marked bronchitis symptoms are permanently present and asthmatic exacerbations also occur, the nitrites give relief to the urgent dyspnœa in a large proportion of the cases, yet by no means in all. The disappearance of the rhonchi in bronchitis under the influence of the nitrites I have often seen, but it does not in my experience occur so frequently as in the cases observed by Fraser.

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[1] *Trans. Ed. Med. Chir. Soc.*, vol.

Where abundant moist sounds are present owing to a large amount of secretion in the bronchial tubes, the nitrites generally are of little service. But in dyspnœa with bronchitis, indicated by abundant sibilant and sonorous rhonchi, and also in asthmatic paroxysms, amelioration is at least the rule; at times paroxysmal dyspnœa is cut short by a single dose of one of the nitrites, and may not recur for hours. In bronchitic dyspnœa the duration of the relief varies, but usually lasts as long as the influence on the circulation. From this Fraser thinks that the nitrites produce their effect by relaxing the muscles of the bronchial tubes, in the same manner as they relax the contraction of the blood vessels, and that this effect is the essential cause of the relief nitrites give in dyspnœa. From the marked effect of nitrites in some cases of asthma and bronchitis, and from the evidence we have of the influence which nitrites exert on involuntary muscle fibre, it certainly seems probable that they are capable of increasing the lumen of bronchial tubes when narrowed by contraction of muscular fibre which surrounds them; but it by no means follows that such contraction is the sole cause of asthmatic paroxysms or the exacerbations of dyspnœa in bronchitis. There is a want of uniformity in the action of nitrites which I should hardly expect if paroxysmal dyspnœa depended entirely upon contraction of the bronchial muscles alone. Moreover, dyspnœic attacks are at times relieved by nitrites without any marked alteration in the auscultatory signs.

It seems to me likely that some alteration takes place in the bronchial mucous membrane more or less coincident with spasmodic contraction of the bronchial muscles.

Sir Andrew Clark[1] has suggested as a cause for asthmatic paroxysms a sudden hyperæmic swelling of the mucous membrane of the bronchial tubes comparable to the changes which occur in the skin in urticaria. Fraser is of opinion that the relief afforded by the nitrites in asthma is opposed to such a theory, because the dilating action on the vessels which he supposes occurs in the bronchi, as in all the other vessels of the body, would increase or prolong the paroxysm instead of controlling or checking it. With this view I cannot coincide; for if the tumidity of the mucous membrane connected with asthmatic attacks resembles that which occurs in urticaria, it is probable that it is associated with spasm; at least in urticaria antecedent spasm is held as probable. It is not likely that vascular dilatation would be present at any one time over the whole mucous membrane affected; it is more probable that spasm and dilatation would coexist in different portions of the mucous membrane. Such a condition the administration of nitrites would tend to relieve. By decreasing spasm they would tend to restore the mucous membrane to its normal condition. It is just possible, too, that the dilating influence exerted on the pulmonary vessels by the nitrites may to some extent relieve the bronchial vessels.

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[1] *Int. Journ. of Med. Sci.*, 1886, p. 105.

As a rule nitrites are well borne by dyspnœic patients, and large doses may be safely given if experience shows they are needed. I have administered 1 drachm of a $2\frac{1}{2}$ per cent. solution of ethyl nitrite every ten minutes, until 3 or 4 drachms have been taken. Sodium nitrite is at times borne better in pulmonary dyspnœa than ethyl nitrite, and sometimes the reverse is the case.

The spiritus ætheris nitrosi of the Pharmacopœia would be equally serviceable if it always contained a definite amount of the ethereal nitrite, but the rapid deterioration in the strength of this ingredient, which at times takes place, renders it uncertain in its influence. Perhaps the best preparation would be liquor trinitrini combined with a small quantity of rectified spirit. Headache, however, seems to me more common after trinitrine than after nitrites. Of late I have used ethyl nitrate in doses of from 5 to 10 minims, and find that it is quite as efficacious as ethyl nitrite, and that its influence lasts longer. Amyl nitrite acts for too short a time to be of service.

The nitrites must not be looked on as curative agents in bronchitis; they are capable often of relieving dyspnœa, and by dilating the vessels of the lung they may possibly temporarily relieve the right heart. But in the ordinary forms of bronchitis their regular administration does not, as a rule, prove very advantageous. It is for the relief of dyspnœic conditions they should be reserved, and even then they often fail when abundant moist sounds indicate that the difficulty of breathing is connected with accumulation of bronchial mucous rather than with spasm of the tubes or vessels. By some the nitrites have been used in pneumonia, lung œdema, and many other lung ailments. It is quite possible that they may give relief at times, but I question whether they can be looked on as curative.

URÆMIC DYSPNŒA.

In uræmic dyspnœa I have been at times disappointed in the use of nitrites. Scattered through the journals are many records of the utility both of nitro-glycerine and amyl nitrite in this condition. I also have found them advantageous, yet they have often failed. They are indeed well borne in large doses, but the relief they give is usually transient. Perhaps it may be that uræmic dyspnœa owns another cause besides those which are the chief factors in cardiac and pulmonary lesions. Huchard is of opinion that even in that altered condition of the arterial walls which often so long precedes renal disease (and which may indeed terminate life by the cardiac troubles it induces, apart from renal disease), toxic products may accumulate in the blood, because the kidney is unable from the changes in its vessels to eliminate them. He adduces in support of his views the non-toxic effect of the urine in these cases, and he looks on the dyspnœa which occurs as the result of the reaction on the body of toxines which would have been eliminated had the kidney been perfectly healthy. In Bright's disease this toxic material must be often present, and it seems possible that in some cases it may exert its influence so strongly as to neutralise the effects of the nitrite molecule, as I have shown barium neutralises it outside the body. There must be great variations in the amount of toxic material present at various times, and it may be this variation accounts for the different effects produced by nitrites under apparently the same conditions. Nitrites and nitro-glycerine cannot be relied upon to combat the high tension which is often present long before renal disease declares itself. They act quickly, but not continuously, for they are easily eliminated. There is reason to believe, too, the tissues get accustomed to them if they are given frequently, and become less influenced by them; hence I believe their frequent administration is not desirable in this condition, which, as Huchard and others have pointed out, should be met by milk diet and eliminants. But to relieve some of the discomforts arising from high tension—as headache, heaviness, and dyspnœa — the administration of liquor trinitrini or the nitrites is often of great service, and in the dyspnœic paroxysms which accompany the heightened tension from arterial changes when cardiac dilatation has commenced, these drugs are of the greatest value if given in sufficient doses.

Let me lay stress on the word "sufficient." The doses in these cases must usually be large, and an amount which will dilate the vessels ordinarily very fully may have too slight an effect to be of service in chronic Bright's disease. Yet, even in this ailment, full doses at times produce alarming symptoms, and even moderate amounts may give rise to discomforts. It is never wise to commence the administration of nitrites and nitro-glycerine with large doses.

CHEYNE-STOKES RESPIRATION.

Filehne, many years ago, noticed that the inhalation of amyl nitrite will remove the Cheyne-Stokes respiration, and attributed its result to its effect on the vasomotor mechanism. Gibson, however, finds that though it has this effect in some cases, owing, he thinks, to its stimulating effect on the central nervous structures, it produced no influence in others[1].

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[1] *Practitioner*, vol. xxxviii., p. 86.

MIGRAINE AND HEADACHE.

For the relief of headache the nitrites and nitro-glycerine have been much employed, and considerable success has been recorded from their use. Amyl nitrite has been specially credited with the power of relieving migraine, and sometimes curing it. That it will at times cut short an attack, no one who has used it extensively as I have done can doubt, but in my hands its failures have far outnumbered its successes. Even if, as has been suggested, the immediate cause of suffering in some forms of migraine is connected with local vascular contraction, it is not likely that a very temporary dilatation of the vessels could be relied on to restore a normal condition. We know, however, how suddenly tension may fall, and inhalation of amyl nitrite coming at the right time may be the final cause of relief, the dilatation which it causes not being followed by contraction. But perhaps, as Pick long ago suggested, it is sometimes probably a kind of "surprise influence," which immediately takes away the pain when nitrite of amyl is inhaled, just as any other influence, physical or mental, may have the same effect. It not infrequently happens that after amyl nitrite inhalation has succeeded once or twice, it subsequently quite fails to give relief. The drug, indeed, has not maintained its promise, the utility attributed to it in the accounts of earlier reporters has not been borne out by frequent use. It does not seem likely that nitrite of amyl can permanently cure migraine.

Nitrite of amyl has been used to combat slight forms of headache; and here, too, it is sometimes successful in giving relief, but, as it at times greatly intensifies the pain, its general employment has fallen into disrepute. Nitro-glycerine is probably a far more effective remedy than amyl nitrite. Dr. Hammond and many others have borne strong testimony to its utility in migraine. It is naturally most useful in those attacks in which the face is pale and the radial artery tense. A drop or two of nitro-glycerine in these conditions I have sometimes seen give rapid and long-lasting relief, yet this effect is by no means always seen, and in neurotic patients and those with low tension and an easily excitable circulation, discomforts may be considerably aggravated. I believe, however, that nitro-glycerine might with advantage be more frequently used for the relief of migraine and headache generally, if care were taken to employ it only where the circulatory conditions point to some degree of high tension. That migraine and other forms of headache have permanently disappeared under its use I do not doubt; it is by no means so certain that this effect has followed because of its use. The dose of nitro-glycerine given for the relief of headache should always be in the first place small. Even a single drop, if the case be not suitable, may prove very unpleasant for the patient. It is sufficient in doubtful cases at least, to commence with half a drop of liquor trinitrini. If slight relief or no relief ensue in half an hour, a drop may be given, and later on, if necessary, larger doses.

NEURALGIA.

In neuralgia, especially of the fifth nerve, the administration of nitrite of amyl and nitro-glycerine has been followed by relief. Considering the trivial circumstances which seem at times both to bring on and to remove neuralgic pain, we can hardly be surprised that agencies which so powerfully affect the circulation should have a distinct influence in this ailment. In the majority of cases both amyl nitrite and nitro-glycerine have in my hands failed to give relief, and it has appeared to me probable that where they have removed pain their success has been due to circulatory influence, to what I have called a "surprise" effect, or to suggestion.

STRYCHNINE POISONING AND TETANUS.

Dr. H. C. Wood has proved that amyl nitrite depresses the reflex influence of the cord, and it has been suggested that this power might be utilised in strychnine poisoning. Experiments have been made which seem to show that in the rabbit nitrite of amyl antagonises to some extent the lethal influence of strychnine;[1] but, as Dr. H. A. Hare points out,[2] to be of service its full physiological action must be continuously present, and inhalation will not suffice. I do not see how this drug can be of any practical use in strychnine poisoning in man, nor is it likely that in tetanus it will prove an available remedy, although some cases have recovered after its use. The long-lasting effect of the tetanus poison cannot, it seems to me, be effectively antagonised by the fleeting action of nitrite of amyl or other nitrites.

EPILEPSY.

In epilepsy nitrites of amyl and sodium have been extensively tried, but the testimony as to their value is by no means uniform. Their employment rests to some extent on pharmacological grounds, for the nitrites in large doses depress the functions of the cerebral cells; they likewise dilate those vessels, the contraction of which is a concomitant—and some have thought a cause—of epileptic seizures. Moreover, it has been shown by Sir J. Crichton-Browne that when the brain of a rabbit rendered epileptic by artificial means is stimulated, convulsions will not follow in the usual manner if amyl nitrite be inhaled.[3] In favour of the utility of nitrite of amyl we have had the testimony of Sir J. Crichton-Browne and Dr. Weir Mitchell. The former found it specially serviceable in the "status epilepticus." Others say they have seen nitrite of sodium advantageous, whilst Osler thinks he has used nitroglycerine with a certain amount of success. But many capable observers believe that the nitrites are of no avail in epilepsy. It seems to me unlikely that substances having such temporary influence on functions and tissues as the nitrites can be of any great benefit. Personally I have not seen good arise from their employment, though I have given them a fair trial. It is, however, possible that the inhalation of amyl nitrite, when an attack is immediately impending, may ward it off. In the case of nitro-glycerine and sodium nitrite, dilatation of the vessels does not, if ordinary doses be given, last more than two or three hours, and even during much of this time the arteries are contracting after their dilatation. Unless, then, nitrites are given at very short intervals, the protective effect must be transient. I do not anticipate that the nitrites will ever play an important part in the treatment of epilepsy.

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[1] St. Clair Gray, *Glasgow Medical Journal*, 1871, p. 166.

[2] *Boston Medical Journal*, vol. cxi., p. 481.

[3] *West Riding Lunatic Reports*, vol. iii., p. 168.

Tinnitus Aurium.

Some evidence has been given that both nitrite of amyl and nitro-glycerine are at times of benefit in tinnitus aurium. I have seen some relief given by nitrites in this ailment, but have not had sufficient experience of its use to speak definitely of its advantages.

Bright's Disease.

I have already given my views as to the diuretic value of nitrites when speaking of their pharmacology; I propose now to allude to their employment in Bright's disease. In acute Bright's disease it is very difficult to determine the effects of a diuretic. Spontaneous increase in the urine flow is as much a part of the natural history of the disease as is the termination of pneumonia by defervescence. In ten cases of acute nephritis, the course of which was not influenced by medicine, I found that in all diuresis set in between the ninth and twenty-first day. I have certainly seen a great increase in the urine flow follow the administration of the nitrites of ethyl and sodium and of nitro-glycerine in many cases of acute nephritis. But, on the other hand, this result by no means always follows, and I know of no means by which it can be determined whether, when a diuresis occurs in acute nephritis after a nitrite, it is *post hoc* or *propter hoc*. General impressions are not of great value, but it certainly has seemed to me that a minim of liquor trinitrini or two grains of sodium nitrite every four hours occasionally expedites the advent of the diuresis which precedes recovery. Such medication, too, may tend to decrease headache and other discomforts present in acute Bright's disease, and I believe there is the advantage that it is incapable of doing harm. No evidence has yet been given that nitrites can inflict any injury even on an inflamed kidney. As I have not found diuresis follow in a very early stage of acute Bright's disease, I do not give them in the earliest stage unless symptoms are present which seem to render their administration desirable; but in the doses I have mentioned they may be useful as adjuncts to other methods of treatment if, after a week or more has elapsed, no critical diuresis supervenes.

In the large white kidney and in mixed forms of chronic nephritis the difficulty of judging of the value of a remedy, though not so great as in acute Bright's disease, is still considerable, for here, too, we not infrequently meet with spontaneous diuresis which is apt to be put down to any medicine that has been given. It has been claimed that nitrites in chronic Bright's disease decrease the total amount of albumen passed whilst they increase the amount of water passed. I have been unable to determine the regular decrease in albumen which some have seen, though decrease at times occurs, nor have I been able to note so great an alteration in the amount of water passed as would lead me to believe that they have a pronounced effect on its excretion. I have indeed, at times, known profuse diuresis occur under their use. But, as in acute Bright's disease, I have not always been satisfied that it has taken place because of their use. I have, indeed, often observed a temporary increase lasting a day or two, and comparing the amount of urine excreted during the periods in which nitrites have been given with the amount passed before and after the administration of nitrites, I find in a series of cases in which the data are fairly reliable, a slight increase in the amount of urine excreted under nitrites. It has seemed to me that under the influence of small doses of nitrites, three or four times a day, patients have been on the whole more comfortable, the skin acting better, and dyspnœic discomforts, if present, becoming less prominent.

My impression, then, is in favour of a use of nitrites in Bright's disease; I do not hold them to be curative, but they seem to give relief.

In the contracted form of chronic Bright's disease, the nitrites are often of great value, especially in the later stages. In the earlier stages, when the chief symptoms are failing health and high tension, I have not seen them of service, but when there is dyspnœa, and the heart's action begins to fail somewhat, a minim of trinitrin solution given three times daily will often add greatly to the patient's comfort, and I believe tend to prolong life, even though it may fail to subdue dyspnœic storms. It is said to be of service in uræmic convulsions; I have not seen definite advantage from it in the few cases in which I have employed it.

OTHER DISEASES OF THE GENITO-URINARY ORGANS.

In dysmenorrhœa nitro-glycerine has been found of service, and it is certainly worthy of a trial. In *post-partum* uterine contractions there are records of advantages gained by its use, but its vascular influence renders it a remedy of doubtful value in these cases.

SEA-SICKNESS.

In the relief of gastric disturbances the nitrites can play but little part; utility has been claimed for them in enteralgia, and they have been given in sickness and the vomiting of pregnancy, like every other conceivable remedy. But it is not easy to see how they can be of service in gastro-intestinal irritation, for neither nitrous acid nor nitro-glycerine are sedatives. The claim of nitrite of amyl and nitro-glycerine for the relief of sea-sickness seems to stand on firmer ground; giddiness from anæmia of the brain is one of the troubles of *mal de mer*, and this may be relieved by nitrites. The pathology of sea-sickness is not sufficiently known to enable us to say that the nitrite influence on the circulation is likely to combat the conditions which give rise to nausea and sickness; only experience can determine their value. It seems to me, however, that the balance is in favour of the occasional efficacy of vaso-dilators, and one or two tabellæ of nitro-glycerine are worthy of trial. The inhalation of amyl nitrite seems to be the most objectionable form in which nitrites can be given for sea-sickness.

I do not propose to deal further with the numerous ailments in which the nitrites and nitro-glycerine have been employed. They are credited with the cure of ailments differing very widely in character, as for example ague, cholera, chorea, and whooping-cough, but a knowledge of their pharmacological properties makes it probable they can only relieve certain symptoms connected with circulatory conditions which may be present in these ailments.

ADMINISTRATION AND DOSAGE.

Before I finish with the therapeutics of the nitrites I should like to make a few remarks on the employment of the official compounds, and especially with regard to the spiritus ætheris nitrosi. When nitrite of sodium was first employed medicinally it was found to be very impure, sometimes containing more than 50 per cent. of the inert nitrate; even now impure specimens are occasionally dispensed. It is important, therefore, that the purity of the drug used should be inquired into if it does not give the relief sought for. With regard to dose, I believe it is well to begin with 2 grains. I have myself never seen discomforts from even 3 grains. But severe throbbing of the head has been recorded after this amount; and, when given regularly, in a very few instances slight blueness of the lips has been reported. Much larger doses may be given if neither physiological effects nor relief follows from the smaller doses; I have raised the dose to 3 or 4, rarely to 6 grains, without seeing evil follow, but occasionally even small doses cause slight stomach discomforts. Solutions of sodium nitrite in the form of mixtures seem to keep fairly well.

The tabellæ trinitrini and the liquor trinitrini are excellent preparations of nitro-glycerine. It should be remembered, however, that nitro-glycerine will under some conditions decompose. In distilled water it undergoes no change, but in the presence of alkalies, nitrite of the alkalies is formed, and when any salt is present some decomposition may occur. It is best, therefore, to order the liquor trinitrini in distilled water. One minim forms an average dose to commence with, but may be gradually raised without fear of injury to 20 minims or more, provided no discomforts follow from its use. A small dose of nitro-glycerine may be repeated if it fail in ten or fifteen minutes to produce a perceptible effect, for in that time its full influence has been usually exerted. A somewhat longer time should be allowed to elapse after sodium nitrite. Nervous and hysterical people often feel throbbing in the head, or even severe headache after small doses of either compound. It is rarely necessary to resort to subcutaneous injections, since nitrite of amyl acts so quickly when inhaled, and nitro-glycerine when taken by the mouth. On one occasion, however, I saw a patient, after severe and prolonged anginal pain, lapse into semi-consciousness. After the failure of amyl nitrite relief seemed at once to follow the injection of 2 minims of liquor trinitrini. I find that nitro-glycerine is preferable to sodium nitrite for subcutaneous injection.

Concerning the value of spiritus ætheris nitrosi there is much difference of opinion. As a household remedy it is much believed in and largely used; as a medicine it is employed usually rather as a routine remedy than because much faith is placed in its action. When in proper strength it contains an amount of nitrite of ethyl sufficient to enable it to reduce tension, yet its proneness to decomposition renders it an unreliable remedy for the purpose. The lack of appreciation of its value is, however, to some extent due to the method in which it is ordinarily employed; it consists of rectified spirit containing in solution about 2 to $2\frac{3}{4}$ per cent. of nitrite of ethyl, an uncertain amount of aldehyde, and minute proportions of ethyl nitrate and other compounds.

I shall point out shortly that aldehyde possesses properties which are in some measure antagonistic to those of ethyl nitrite; it contracts vessels, whilst nitrites, as we have seen, dilate them. Ethyl nitrate acts in the same direction as ethyl nitrite, but it is to the latter compound that spirit of nitrous ether owes its influence on the circulation. Now spirit of nitrous ether, when not exposed to the air, does not undergo rapid change in constitution, but kept, as it often is, for dispensing purposes, it rapidly loses some of its nitrite element. I found, for example, a half-filled bottle, which, on the day I first examined it contained the official amount of ethyl nitrite, lost in thirteen days 16 per cent.

Many cases have been mentioned in which spirit of nitrous ether has been found to contain less than one-tenth of normal amount of nitrite. But, owing to the method in which it is usually given, it becomes still more unreliable as a remedial agent. Under any circumstances, a considerable portion of the nitrite of ethyl which it contains (about 50 per cent.) is at once dissipated, but, on keeping the mixture, the loss continues until all the ethyl nitrite is dissipated or decomposed. If, for example, half an ounce of spiritus ætheris nitrosi is mixed with 4 ounces of water, about half of the active ingredient—the nitrite of ethyl—

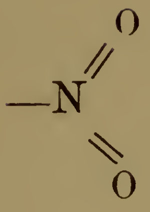
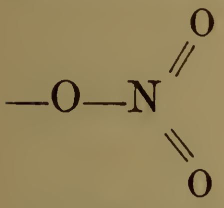
is usually at once dissipated. But it will be found that on the next day 30 to 50 per cent. of what was left has gone, and on the third day the mixture will probably contain a very small amount of the ethyl nitrite. The rapidity of disappearance varies greatly according to temperature and other circumstances, but it is manifest that, under these conditions, mixtures containing spirit of nitrous ether soon lose any medicinal value which when first dispensed they may have. To be effective, spiritus ætheris nitrosi should be taken immediately it is mixed with water. A mixture becomes less effective with each dose taken.

An alkali, or the acetate or citrate of ammonia, prevents, to a large extent, this loss of nitrite. It is on this account, perhaps, that the old-fashioned fever mixture, containing acetate of ammonia and spirit of nitre, has justly maintained for so long a time its reputation as a diaphoretic and diuretic.

In combining spirit of nitrous ether, or the nitrites, with other medicines the short period of their activity must be remembered. It has been suggested that the contraction of the vessels due to digitalis might be counteracted by combining it with the nitrites. Undoubtedly the contraction caused by digitalis may for short periods of time be annulled, but the prolonged action of digitalis on the vessels cannot be fully antagonised by substances like the nitrites.

Chapter VI.

THE NITRO-COMPOUNDS.

The group  $-\mathrm{N}\begin{array}{l}/\!\!/\,\mathrm{O}\\ \backslash\!\!\backslash\,\mathrm{O}\end{array}$, in which nitrogen is probably a pentad, as it is in the nitrate group, is capable of replacing a molecule of hydrogen in both fatty and aromatic compounds, and it seems of interest to determine whether this group plays an active part in the compounds into which it enters like the nitrite group ($-\mathrm{O}-\mathrm{N}=\mathrm{O}$ with which it is isomeric, or a more passive part like the nitrate group  $-\mathrm{O}-\mathrm{N}\begin{array}{l}/\!\!/\,\mathrm{O}\\ \backslash\!\!\backslash\,\mathrm{O}\end{array}$. I have examined the action of the following paraffinic nitro-compounds on muscles, on vessels, and on the heart: Nitro-methane CH_3NO_2, nitro-ethane $C_2H_5NO_2$, nitro-propane $C_3H_7NO_2$, and nitro-pentane $C_5H_{11}NO_2$. The nitro-paraffins are colourless compounds boiling above 212°, slightly soluble in water, and very stable. They break up in the presence of alkaline carbonates, nitrites of the metals being formed.

Professor Dunstan[1] has pointed out that when nitro-ethane is mixed with potassium carbonate half its nitrogen appears as nitrite of potash; it is decomposed by the carbonates even in the cold. The higher compounds are much less easily decomposed by alkalies than the lower.

Action on the Muscles.

I find that nitro-methane has but little effect in interfering with the contractile power or life of muscle. If one part be added to 500 of normal salt solution the contractions do not seem in any way interfered with. Nitro-ethane is equally free from toxic effects; a muscle put up in a normal salt solution containing 1 in 500 of nitro-ethane was contracting well at the end of 290 minutes. In 1 in 1,000 a muscle was living and would contract to stimulation after twenty-six hours. Nitro-propane is slightly more toxic than nitro-ethane; 1 part of nitro-propane in 1,000 parts of normal salt solution causes the contractions to fall somewhat at the end of 270 minutes, but the muscle will live twenty-four hours. One part of nitro-pentane is not soluble in 1,000 parts of salt solution, but it is distinctly more toxic, for the muscle will not contract in a saturated solution more than six hours. (Fig. 149). Moreover, a certain amount of contracture is sometimes produced, as in the case of many of the amyl compounds.

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[1] *Journal of Chemical Society*, 1891.

Action on Vessels.

In a strength of 1 in 1,000 nitro-methane always dilates the vessels of the tortoise slightly. In a typical experiment a flow of 11 c.c. through the vessels was increased to 15, an increase of 36 per cent. (see Fig. 144).

With nitro-ethane I got some rather contradictory results. In one case, from causes which I cannot explain, contraction occurred; on other occasions always dilatation. But the amount of this dilatation varied; sometimes it was not greater than with nitro-methane, in other cases the flow increased to more than 100 per cent. (see Fig. 147).

On the whole, the dilating power of nitro-ethane was distinctly greater than that of nitro-methane. Nitro-propane always very markedly dilated the vessels, the increased flow exceeding 100 per cent. (see Fig. 148). Nitro-pentane is very insoluble in water, the very minute quantity which is soluble (probably not more than 1 in 5,000) dilates the vessels, but not so much as nitro-propane.

On the heart of the frog nitro-methane in the strength of 1 in 1,000 has practically no effect. It may, perhaps, beat a little more quickly, but this is the only influence exerted. Nitro-ethane quickens the heart's action, and renders the beat less forcible. (Fig. 145). Nitro-propane, 1 in 1,000, often doubles the speed of the heart beat, and weakens it considerably. It is impossible, as I have said, to dissolve 1 in 1,000 of nitro-pentane, for it is more insoluble than the other nitro-compounds, but a saturated solution both quickens and weakens the heart's action.

Effects on Circulation.

The effects I have so far noticed on the vessels, muscles, and heart are due directly to the nitro-compounds themselves. The saline solution in which the muscles have been contracted, and the fluid which has passed through the vessels in the perfusion experiments, have always been tested for nitrites before and after each experiment, but no trace of nitrites has been found, nor has the blood used for the heart experiments shown, by the presence of methæmoglobin,that nitrites have taken any part in the production of increased rapidity and decreased power. No nitrite is formed immediately when nitro-compounds are mixed with weak alkaline solutions in the cold, but when heat is applied nitrites are in time produced. On mixing, for example, one part of each of the four nitro-compounds with 50 of a 5 per cent. solution of sodium carbonate, I detected no nitrite immediately, nor did I find any after keeping the mixtures at 38° for 40 minutes, but in a few hours the presence of a nitrite was detected in all.

When nitro-ethane is mixed with blood at ordinary temperatures, methæmoglobin is not formed until decomposition sets in, but if the mixture be kept at 38° it appears after some hours.

As in the case of nitrates, it seems possible that nitrites are more readily produced after absorption into the circulation, at least an effect on the tension, somewhat like that caused by nitrites, follows. When 15 minims of nitro-ethane are given by the mouth and the tracing is continuously watched, no distinct change is perceived for about a quarter of an hour, then a slight lowering of tension occurs. In 30 minutes this is distinct, hence onwards for nearly four hours the lowered tension continues, but I have not found the same extent of fall produced as after either nitrites or nitrates; on the other hand the fall is much more prolonged, and may not reach its lowest point until three or four hours after the drug has been given (see Fig. 146). Sometimes at the end of five hours the tension is still lowered, at other times it has risen to its normal height in four hours.

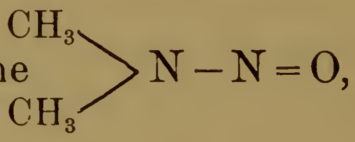
Nitro-propane, in a dose of 15 minims, has much the same effect as nitro-ethane; for a short time it seems to have but little influence on the pulse, but in three or four hours the tension has become distinctly lowered, and it is five or six hours before the pulse regains its normal condition. After 10 minims of nitro-pentane I noticed the first fall of tension in about thirty minutes, but it was seventy minutes before any distinct fall took place. Between three and four hours after the drug had been taken the tension reached its lowest point, and the pulse had not quite regained its normal condition in six hours. (See Fig. 150). Very slight effect is produced on the frequency of the pulse by the fatty nitro compounds; sometimes, but not always, during the lowered tension it is raised 5 to 10 beats per minute. No headache has been complained of by those who have taken these drugs, and no subjective symptoms have been noticed, but my experience of their effects is not yet sufficiently wide to say that headache and palpitation may not in some be produced.

I have not so far proved that in the living body nitro-compounds can be decomposed and nitrites produced; the changes which take place both when nitrates and nitro-compounds are mixed with blood is a subject I propose to investigate further; but either from the gradual development of nitrites, or from the action of the whole molecule itself, the fatty nitro-compounds possess a power of slowly depressing tension and keeping it down for a lengthened period, which may be found useful in therapeutics provided no bar to their utilisation appears. For the relief of angina pectoris, of course, they can be of no service; to prevent attacks in this ailment, and for the relief of some conditions connected with rise in tension, they may prove of value.

The NO_2 group does not give a toxic influence to the fatty compounds into which it enters. It differs completely in this respect from the ONO group, and resembles the ONO_2 group. Dr. Brunton has made experiments to determine its action in nitro-benzine, in which compound NO_2 replaces an atom of hydrogen. When benzine, C_6H_6, is injected into the frog it causes some lethargy, and renders the spinal cord more excitable, as shown by tremor on movement, eventually paralysing it. Nitro-benzine, $C_6H_5NO_2$, caused the same symptoms; the tremor seemed a little greater and the reflexes were abolished a little earlier, but the experiment showed that, so far as the aromatic compound benzine was concerned, the nitro-group plays almost as passive a part as it does in the compounds of the fatty series.

NITROSAMINE GROUP.

In the Nitrosamine group ($=N-N=O$) an atom of nitrogen replaces one of the atoms of oxygen in the nitroxyl group, and has two links left free for junction with two other groups. It seemed interesting to determine what effect this group would have as compared with the group $-O-N=O$, when joined to fatty radicles. The effect of the junction is to produce a series of liquids extremely unpleasant to smell and taste, soluble in alcohol, and also slightly in water.

I have experimented with the dimethyl-nitrosamine, diethyl-nitrosamine and di-isobutyl-nitrosamine compounds. The action of the NNO group in no way resembles that of the ONO group, and, notwithstanding their nauseous smell and taste, the nitrosamines are not poisonous to the tissues. Dimethyl-nitrosamine  $\left.\begin{matrix}CH_3\\CH_3\end{matrix}\right> N-N=O$, is not fatal to muscle in the strength of 1 in 1,000, and the diethyl-nitrosamine is equally innocuous, but when the butyl element takes the place of methyl or ethyl the resulting compound, di-isobutyl-nitrosamine, will, in the strength of 1 in 1,000, kill the muscle in about two hours.

The diethyl- and dimethyl-nitrosamines have no influence on the vessels; in the strength of 1 in 1,000 they do not either contract them or dilate them (see Fig. 151). They slightly quicken the isolated heart and then weaken it in the strength of 1 in 1,000, but this organ bears the presence of the ethyl and methyl compounds quite well.

I have not tried the effect of the nitrosamine compounds on the general circulation; their nauseous character renders it manifest they can never be of practical therapeutic importance, and whilst I have had volunteers willing to take nitrate, nitrite, and nitro-compounds, no one after once tasting the nitrosamines desired to go further. The chief point of interest in connection with their action on the various tissues is their harmlessness. The butyl compound killed muscle rapidly, but this is to be expected where there are two butyl molecules.

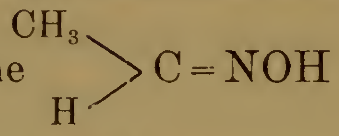
THE HYPONITRITE GROUP.

In most books on chemistry the existence of hyponitrites is alluded to, and hyponitrous acid is represented as having the formula HNO, the sodium salt being represented as NaNO.

It would have been highly interesting, had this been the case, to have ascertained the difference of the influence of the group NO and ONO in the respective compounds they form with sodium and the fatty radicles. Zorn, however, from his investigations on hyponitrous ether, has come to the conclusion that the hyponitrites are, as I have said in my first lecture, diazo-compounds, consisting of two molecules of the group NOH, the nitrogens of which are united by a double link. It seemed to me, nevertheless, of interest to determine, if possible, the comparative effect on tissues even of this double group as compared with the group ONO. Unfortunately the sodium hyponitrite is extremely unstable, solutions readily decomposing, free soda being left in the solution which becomes very alkaline. It is very difficult, therefore, to judge how far the effect produced by sodium hyponitrite is due to the hyponitrite molecule or to free soda. I find that 1 of sodium hyponitrite in 1,000 of normal salt solution will kill the gastrocnemius of a frog in an hour. When perfused through the tortoise the vessels contracted so strongly as entirely to stop all fluid passing through them. The beats of the heart were rendered irregular and slow when 1 of sodium hyponitrite in 1,000 of blood was passed through it. The experiments I have made are, however, of doubtful value, because of the free alkali present. The neutralisation by hydrochloric acid of the hyponitrite saline solution altered the shape of the muscle tracing, which, with the alkaline hyponitrite solution, had the appearance usually seen after alkaline solutions, but did not materially diminish toxicity.

THE OXIME GROUP.

Of late years a large and chemically interesting group of compounds have been produced, called "oximes," which contain the group NOH united by a carbon element either to two fatty radicles or to one fatty radicle and hydrogen.

Aldoxime  $\left.\begin{matrix}CH_3\\H\end{matrix}\right>C=NOH$ is one of the best known examples of this group.

If CH_3 is replaced by ethyl C_2H_5, propyl aldoxime is formed. Isobutyl and other homologous oximes can in the same manner be produced by replacing C_2H_5 by higher members of the fatty series. At my suggestion two years ago Dr. Pomfret, at that time one of the Berkeley Fellows in Pharmacology, investigated in my laboratory at Owens College the effect of a series of these oxime bodies with a view of ascertaining how far they possess any pharmacological type which can be referred to the presence of this group in their structure. I propose to refer briefly to the action of three of them in order to illustrate the influence of the NOH group.

Aldoxime or ethyl aldoxime is a colourless fluid miscible in all proportions with water; it is remarkably free from all poisonous action on skeletal muscle. The gastrocnemius of a frog will live in a mixture 1 part of aldoxime in 200 of normal salt solution for twenty-four hours. In solution of more than 1 per cent. contracture is produced, but even in 1 in 50 a muscle will live more than two hours. Propyl aldoxime (C_3H_6NOH) acts on skeletal muscle like ethyl aldoxime, but contracture is produced by more dilute solutions. It is also more toxic. In a solution of 1 in 200 a muscle lived over four hours.

Isobutyl (C_4H_8NOH) aldoxime is still more toxic to muscle. A muscle dies in 1 part of this compound to 200 of normal salt solution within an hour. Contracture comes on more quickly, and is more marked than with either the ethyl or propyl compounds.

On the blood vessels of the tortoise the effects of ethyl aldoxime vary with the strength of the solution: 1 in 1,000 always increases its flow (Fig. 152): stronger or weaker solutions usually cause a primary contraction followed by slight secondary dilatation.

Propyl aldoxime invariably dilates the vessels. The dilatation is much greater than that brought about by ethyl aldoxime. (Fig. 153). Isobutyl aldoxime in weak solutions also dilates the vessels. In the perfusion of organs of warm-blooded animals Pomfret noted that a different effect is produced on the vessels according to the time which elapses between adding aldoxime to the blood and perfusing it. When blood is mixed with aldoxime shortly before perfusion a primary contraction of the vessel is invariably obtained. If the blood and aldoxime stand in an open vessel for two or three hours dilatation at once results. This fact led him to make an examination of the effects of aldoxime on blood, and he then found that though on adding aldoxime to blood no change at first takes place, after standing for a few hours the blood darkens, and the spectroscope shows that this darkening is due to the presence of methæmoglobin. At the temperature of the body methæmoglobin is produced in 15 to 20 minutes. From further examination he found that aldoxime, when mixed with blood, breaks up into hydroxylamine and aldehyde. Hydroxylamine has been shown to form in alkaline fluids a nitrite of the alkaline metal, and thus the addition of aldoxime to blood leads to the formation in it of aldehyde and nitrite of sodium. Pursuing his research he investigated the physiological properties of the aldehyde group, and discovered that aldehydes have a directly opposite effect to that of the nitrites; they stimulate muscles and contract vessels. When the perfusion of warm blood containing aldoxime through an organ takes place soon after the aldoxime is mixed with the blood, the presence of aldehyde causes the vessels to contract. If some time is allowed to elapse the aldehyde, being volatile, escapes, and the nitrites which have been formed dilate the vessels.

The action of propyl and isobutyl aldoxime on the vessels of warm-blooded animals does not materially differ from that of aldoxime. On the heart aldoxime has very little effect; there is an increased rate of beat and an increased heart tonus. Strong solutions sometimes arrest the heart in systole, sometimes in diastole, the varieties being due to the same decomposition which has been noticed in the perfusion of blood. The longer the aldoxime remains in contact with the blood, the less is the tendency to systolic contraction, the greater the tendency to diastolic arrest. The other oximes, propyl and isobutyl, also produce acceleration of the rhythm, but have slightly depressant action. Strong solutions, 1 in 200 of propyl aldoxime did not diminish the amplitude of beat after three hours. Isobutyl aldoxime was much more poisonous.

On the circulation generally aldoxime has but a slight effect. The increased tone which is produced by it in the isolated heart of the frog is not seen in warm-blooded animals because of the formation of hydroxylamine and nitrites, but instead a slight lowering of tension is seen about twenty to thirty minutes after the drug has been taken.

The NOH molecule also joins with or enters into aromatic groups. Dr. Pomfret has investigated the action of quinoxime (C_6H_4ONOH), of salicyl aldoxime ($C_6H_4OHCHNOH$), and benzaldoxime (C_6H_5CHNOH). He finds that the effect of the group NOH in producing contraction of the muscle is seen in these aromatic groups, and that all dilate the vessels.

I have given a very brief account of the results obtained from an examination of the fatty compounds containing the NO, N—NO, and NOH groups, because though what has been noted concerning them is interesting as giving an indication of their influence, the compounds themselves are not likely to prove of any therapeutic value. It is quite possible, however, that amongst the aromatic compounds which contain the oxime group, we may find substances of some utility, but these I have not myself examined.

SUMMARY.

The investigations I have so far made with the view of determining the influence of the groups containing nitrogen and oxygen are, as I said in my first lecture, only preliminary. To determine accurately the action of a group of molecules, we must compare the effects of a large number of compounds containing them, both in the fatty and aromatic series, and we must compare these effects, too, not only on muscles, vessels, and heart, but on all the tissues and organs of the body. This is a work which involves very large expenditure of time. I have ventured, however, to bring forward the results so far obtained.

It has long been known that the influence of certain elements in a compound varies according to the number of affinities by which they are united with other elements in the compound, and the groups I have alluded to seem to furnish an example of this.

For reasons into which I need not enter here, chemists are of opinion that in the nitroxyl or nitrite group nitrogen is a triad element, whilst in the nitrate and nitro groups it is pentad. It may be to this, as well as to the different manner in which two oxygens combine with the nitrogen in the nitrite and nitro groups respectively, that we must attribute the marked difference in their effects. It will be noted that there is some evidence that the hyponitrite group, in which nitrogen also plays the part of a triad, is distinctly toxic, like the nitrite group. The instability of the two triad nitrogen groups may enter to some extent into the causation of their toxicity, but for reasons which I have given it seems to me that, in the case of the nitrite group at least, the molecules of the group itself in some way or other play a definite part in the physiological effect which the compound containing them produces. The addition of another nitrogen to the group NO completely changes the influence which the group NO has by itself, or when associated with another atom of oxygen. The addition of a hydrogen element to the NO group seems equally to modify its influence. The nitrosamines, so far as they have been examined, affect the tissues very slightly. The oximes, at least those of the fatty series, are singularly free from poisonous properties, but the NOH group shows a peculiar influence on muscle contraction. Throughout the experiments the increasing toxicity of the fatty series as the weight of the molecule increases has been very marked. The toxic action of the pentane and butane compounds has been always distinct.

A very remarkable feature has been the influence which compounds containing propyl have in dilating vessels. Nitrate of propyl has singular power in this respect; nitro-propane dilates more than any other of the nitro-compounds, and Dr. Pomfret found that of the aldoximes, propyl aldoxime was the most efficient vessel dilator. Butyl and amyl compounds, if used in the same strength as the propyl compounds, contract instead of dilating vessels; they seem to act as irritants to muscular tissue unless in very dilute form, and the contracture which I have noticed as often occurring with amyl compounds shows that an analogous effect is produced on voluntary as well as on involuntary fibre.

In conclusion, let me say it has not been in any way my purpose to search for new remedial agents, but it seems possible a use may be found for some of the compounds I have examined. I allude to the nitrates and the nitro-compounds. They resemble in their powers the nitrites which we have so long been accustomed to use; probably, indeed, their influence is due to the development of nitrites from them. Yet if they possess the pharmacological properties which, from the examination I have so far made, they seem to have, they may possibly be advantageously employed when we want to influence the vessels more or less markedly for a long time.

It has been said with truth that what is now wanted is not a further supply of new remedies, but a better knowledge of the way in which to use the old ones. It seems to me, however, that if therapeutic knowledge is to advance, we must acquire more information than we now possess as to the exact method in which these older remedies act, we must know how they break up in the body, and we must know, too, the new and often simpler combinations they are capable of forming and how these act. The exact method in which the complex compounds of the organic kingdom influence the body we have not yet sufficient knowledge to comprehend; it is with the simpler compounds we must commence investigations, but a wider and deeper knowledge of the effect of these simpler compounds will surely open the way for the acquirement of further information with regard to the more complex ones. At present, even concerning the simple ones our knowledge is very small. It was with the hope of making some slight addition to this knowledge that the work on which these lectures are based was commenced.

BIBLIOGRAPHY.

BIBLIOGRAPHY.

NITRIFICATION AND NITRITES GENERALLY.

NITRITES OF METALS.

1869. Gamgee (A.). "Researches on the blood. On the action of the Nitrites on the blood." Edinburgh. *Practitioner,* Vol. II., pp. 353-354. *Trans. Roy. Soc. Edin.*, May 7th, 1868, p. 389.

1870. Rabuteau. "Recherches sur les métamorphoses et l'elimination des azotites." *Compt. Rend. Soc. de Biol.*, 1869, Paris, 1870, 5th S., Vol. I., p. 66.

1879. Barth. "Toxicological observations on saltpetre." Dessau.

1879. Crofton (D.). "On the therapeutic effect of the inhalation of the fumes of burning nitre paper in asthma." *Med. Press & Circ.*, Lond. (n.s.), Vol. XXVII., p. 283.

1879. Lösecke (A.). "Ueber Bildung und Bedeutung des salpetrigsauren Ammoniaks." *Arch. d. Pharm.*, Halle, 3 R., Vol. XIV., pp. 54-58.

1880. Fröhner (E.). "Experimentelle Untersuchungen über den Chilisalpeter, vom physiologischen, therapeutischen und sanitätlichen Standpunkte aus." *Repert. d. Thierh.*, Stuttgart, Vol. XLI., pp. 200, 241.

1880. Binz (C.). "Ueber einige neue Wirkungen des Natriumnitrits." *Arch. f. exper. Path. u. Pharmakol.*, Leipz., Vol. XIII., pp. 133-138.

1880. Reichert (E. T.). "On the physiological action of the Potassium Nitrite." With a note on the physiological effects on man by Weir-Mitchell. *Amer. Journ. Med. Sci.*, Phila. (n.s.), Vol. LXXX., pp. 158-180.

1881. Röhmann. "The examination of the urine for Nitrites." *Zeit. f. phys. Chemie.*, Vol. V. pp. 94, 233.

1882. Davy (S. W.). "On a new and expeditious method for the determination of the Nitrites under different circumstances." *Chem. News*, Lond., Vol. XLVI., p. 1.

1883. Alcock (R.). [et al.]. "The Sodium Nitrite research." *Med. Times and Gaz.*, 1883, Vol. II., p. 636.

1883. Baines (A. H.). "On Nitrite of Sodium in the treatment of epilepsy and as a toxic agent." *Lancet*, 1883, Vol. II., p. 945.

1883. Collier (W.). "A case of angina pectoris treated with Nitrite of Sodium." *Lancet*, 1883, Vol. II., p. 901.

1883. Hay (M.). "Nitrite of Sodium in the treatment of angina pectoris." *Practitioner*, Vol. XXX., pp. 179-194, 321-330. Also *Brit. Med. Journ.*, 1883, Vol. II., p. 1095.

1883. Hénocque (A.). "Etude spectroscopique de l'action du nitrite de sodium sur le sang; déductions physiologiques, toxicologiques et thérapeutiques." *Compt. rend. Soc. de Biol.*, Paris, 7th S., Vol. V., pp. 669-673.

1883. Huchard (Henri). "Propriétés physiologiques et thérapeutiques de la trinitrine." (Note sur l'emploi du nitrite de sodium.) Paris. Also *Bull. Gen. de Thérap.*, Paris, Vol. CIV., pp. 337-348.

1883. Huchard. "Action toxique du nitrite de sodium." *B. et M. Soc. de Thérap.*, Paris, 2nd S., Vol. X., pp. 207-209.

1883. Ralfe (C. H.). "Seventeen cases of epilepsy treated with Sodium Nitrite." Abst. *Proc. Roy. M. and Ch. Soc.*, Lond., 1882-3 (n.s.), Vol. I., pp. 23-30.

1883. Ringer (S.) & Murrell (W.). "On Nitrite of Sodium as a toxic agent." *Lancet*, 1883, Vol. II., p. 766.

1884. Destrée. "Des composés nitreux et . . . . du nitrite de sodium dans . . . . epilepsie." *Journ. de Med. Chir. Pharm.*, Brux., Vol. LXXVIII., pp. 100, 252.

1884. Fuchs (P.). "Ueber die therapeutische Wirksamkeit des Natrium-nitrits." Berlin.

1884. Giacosa (P.). "Sur la transformation des nitrites dans l'organisme." *Ztschr. f. physiol. Chem.*, Strassb., 1883-4, Vol. VIII., pp. 95-113.

1885. Lublinski (W.). "Ueber die therapeutische Wirksamkeit des Natrium-nitrits u. des Nitro-glycerins." *Deut. med. Woch.*, Berlin, Vol. XI., pp. 65, 85.

1885. Schweinburg (L.). "Beiträge zur therapeutischen Wirkung des Natrium-nitrits." *Wien. med. Presse.*, Vol. XXVI., pp. 464, 529.

1885. Simon (R. M.). "The therapeutic use of Sodium Nitrite." *Birmingham Med. Rev.*, Vol. XVII., pp. 74-80.

1886. Dipski (Basil). "O farmakolog. dieistvii natrium-nitrita (natrium nitrosum)." St. Petersb.

1887-8. Atkinson (G. A.). "The pharmacology of the Nitrites and Nitro-glycerine." *Phila. Med. Times*, Vol. XVIII., pp. 260-264. *Journ. Anat. and Phys.*, Lond., Vol. XXII., pp. 225, 351.

1887-8. Fraser (T. R.). "The dyspnœa of asthma and bronchitis; its causation and the influence of Nitrites upon it." *Amer. Journ. Med. Sci.*, Phila. (n.s.), Vol. XCIV., pp. 393-415; and Vol. XCV., pp. 122-135.

1887. Mairet (A.) & Combemale. "Recherches sur l'action physiologique du nitrate de potasse et sur le mécanisme de cette action." *Compt. rend. Soc. de Biol.*, Paris, 8th S., Vol. IV., pp. 57-59.

1888. Roosevelt (J. W.). "Cobalto-nitrite of Potassium. Preliminary note on some of its therapeutic effects." *New York Med. Journ.*, Vol. XLVIII., p. 197.

1889. Binz (C.). "Narkotische Wirkungen von Hydroxylamin und Natrium-nitrit." *Arch. f. path. Anat., &c.*, Berlin, Vol. CXVIII., 121-136.

1888-9. Brunton (T. L.) & Bokenham (J.). "On the comparative action of Hydroxylamin and Nitrites upon blood-pressure." *Proc. Roy. Soc.*, Lond., Vol. XLV., p. 352.

1889. Collischonn. "Zwei Fälle von Vergiftung mit salpetrigsaurem Natrium." *Deut. med. Woch.*, Leipz., Vol. XV., p. 844.

1889-90. Frankland (P. F.) & Frankland (Grace C.). "The nitrifying process and its specific ferment." *Proc. Roy. Soc. Lond.*, Vol. XLVII., pp. 296-298; *Chem. News*, Lond., Vol. LXI., p. 135.

1889. Sykes (W.) & Twigg (F. G.). "Case of Poisoning by new 'Sicherheit' explosive." *Brit. Med. Journ.*, 1889, Vol. II., p. 127.

1890. Cohen (S. S.). "Two cases illustrating the therapeutic uses of the Nitrites." *Phila. Hosp. Rep.*, Vol. I., pp. 158-164.

1890. Winogradsky (S.). "Recherches sur les organismes de la nitrification." *Ann. de l'Inst. Pasteur*, Paris, Vol. IV., pp. 213-231, 257-275, 760-771. Also 1891, Vol. V., pp. 92-100, 577-616.

1890. Winogradsky (S.). "Sur les organismes de la nitrification." *Compt. rend. Acad. d. Sci.*, Paris, Vol. CX., pp. 1013-1016.

1891. **Hoppe-Seyler.** "The examination of the urine for Nitrites." *Handbuch*, 5th Ed., p. 356.

1891. **Frankland** (P. F.) & **Frankland** (Grace C.). "The nitrifying process and its specific ferment." *Phil. Tr.*, 1890, Lond., 1891, Vol. CLXXXI., pp. 107-128.

1891. **Bordier** (H.). "Recherches sur la nitrification; étude expérimentale du rôle de la circulation de l'air atmospherique par thermo-diffusion à travers les corps poreux." *Mem. Soc. d. Sci. Phys. et Nat. de Bordeaux*, pp. 185-238.

1891. **Warington** (R.). "On Nitrification." *Journ. Chem. Soc.* Lond., Vol. LIX., pp. 484-528.

1891. **Winogradsky** (S.). "Sur la formation et l'oxydation des nitrites pendant la nitrification." *Compt. rend. Acad. d. Sci.*, Paris, Vol. CXIII., pp. 89-92.

1892. **Winslow** (K.). "Nitrites; their therapeutic action and scope in medical practice." *Boston Med. and Surg. Journ.*, Vol. CXXVI., pp. 353-357.

1893. **Cash** (J. T.) & **Dunstan** (W. R.). "The physiological action of the nitrites of the paraffin series, considered in connection with their chemical constitution." *Phil. Tr.*, 1893, Lond., 1894, Vol. CLXXXIV. (B.), pp. 505-639.

1893. **Leech** (D. J.). "The Croonian Lectures on the pharmacological action and the therapeutic uses of the Nitrites and allied compounds." *Lancet*, 1893, Vol. I., p. 1499; Vol. II., pp. 3, 76, 123, 177. Also *Brit. Med. Journ.*, Vol. I., p. 1305; Vol. II., pp. 4, 56, 108, 169.

1893. **Newell** (J.). "Some of the uses and abuses of the Nitrites." *Canada Lancet*, Toronto, 1893-4, Vol. XXVI., p. 327.

1894. **Sharp** (G.). "Sodium Nitrite as a therapeutic agent." *Practitioner*, Lond., Vol. LII., pp. 345-357.

1895. **Bradbury** (J. B.). "Some new vaso-dilators." *Lancet*, 1895, Vol. II., p. 1205.

1897. **Marshall** (C. R.). "On the antagonistic action of Digitalis and the members of the nitrite group." *Journ. of Physiology*, Camb., Vol. XXII., p. 1.

NITRITE OF ETHYL.

1735. **Pott** (Joh. Heinr.). "Diss. de acido nitri vinoso." Erft. (Exercit. chym. Berol, 1738.)

1743. Cartheuser (Joh. Fr.). "Diss. de dulcificat. spiritum acid. min." Frft. ad Viadr.

1743. Junker (Joh.). "Diss. de acid. dulcificat." Hal.

1745. Sebastiani (G. H.). "Diss. de nitro ejusque relationibus et modo cum ejus acido oleum naphthae parandi." Erft.

1753. Juch (Herm. Paul). "De acido nitri vinoso." Erft.

1761. Henkel (G. M. G.). "Diss. de naphtha nitri etiam per ignem elaboranda." Erft.

1765. Nonne (J. P.). "De naptha vitrioli et nitri." Erft.

1831. Mial. *Edin. Med. and Surg. Journ.*, Vol. XXXV., p. 452.

1848. Strumpf (F. L.). *System. Hand. der Arzneimittel.*, Berlin, Vol. I. (On Sp. Æth. Nit., p. 1013, etc.)

1865. Tichborne (C. R. C.). "On the estimation of Nitrites in the presence of Nitrates." *Pharm. Journ.*, October, p. 201.

1865. Miller (J. S.). "On the estimation of Nitrite of Ethyl." *Pharm. Journ.*, September 1st, p. 95.

1867. Richardson (B. W.). "Action of Nitrite of Ethyl." *Brit. For. Med. Chir. Rev.*, Vol. XL., p. 259.

1878. Hill (T. W.) "Poisoning from an overdose of sweet spirits of Nitre, resembling a case of acute alcoholic poisoning." *Lancet*, 1878, Vol. II., p. 766.

1879. Dupré (A.). "Note on the examination of Spiritus Ætheris Nitrosi." *Analyst*, Lond., Vol. IV., pp. 121-124. *Pharm. Journ.*, Vol. X., p. 93.

1879. Muter (J.). "On the estimation of Ethyl Nitrite in Spiritus Ætheris Nitrosi." *Analyst*, Lond., Vol. IV., pp. 124-126.

1880. Peyrusson. "Sur l'emploi de l'azotite d'ethyle pour assainir les locaux contaminés." *Compt. Rend. Acad. d. Sc.*, Paris, Vol. XCI., p. 338.

1881. Guillaumet (Jean-Albert). "De l'azotite d'ethyle et de son emploi médical comme antiseptique et désinfectant." Bordeaux.

1881. Peyrusson (E.). "De l'action des vapeurs d'azotite d'ethyle sur les impuretés qui sont dans l'air." *J. Soc. de Méd. et Pharm. de la Haute Vienne*, Limoges V., 53-60.

1882. Vallin (E.). "Recherches sur la valeur désinfectante de l'ether azoteux." *Rev. d'Hyg.*, Par., Vol. IV., pp. 207-216.

1883. Leech (D. J.). "Spiritus Ætheris Nitrosi." *Practitioner*, Lond., Vol. XXXI., pp. 241-249.

1883. Hay (Matthew). "The value of some Nitric, Nitrous and Nitro Compounds in angina pectoris." *Practitioner*, Vol. XXX., pp. 321-330.

1884. Dott (D. B.). "The assay of sweet spirit of Nitre." *Pharm. Journ.*, Vol. XIV., p. 819.

1887. Broglio (C.). "Contributo allo studio dell'azione terapeutica dell'etere nitroso dell'etildimetil-carbinol." *Gazz. d. Osp.*, Milano, Vol. VIII., pp. 450-452.

1888-9. Leech (D. J.). "Nitrite of Ethyl." *Med. Chron.*, Manchester, Vol. IX., pp. 177-182.

1889. Painter (E.). "Spirit of Nitrous Ether." *N. York Med. Journ.*, Vol. XLIX., p. 518.

NITRITE OF AMYL.

1859. Guthrie. "Amyl-nitrite." *Quarterly Journal of the Chem. Soc. of London*, Vol. XI., p. 245.

1865. Richardson (B. W.). "On the physiological action of the Nitrite of Amyl." *Report of British Association for the Advancement of Science for* 1864. Also *Med. Times and Gaz.*, 1863-64.

1869. Brunton (T. L.). "Ueber die Wirkung des salpetrigsauren Amyloxyds auf den Blutstrom." *Königl. Sächs. Gesellsch. d. Wissensch.*

1869. Leishman. "Amyl-nitrite in angina pectoris." *Glasgow Med. Journ.* (n.s.), Vol. XIV., p. 556, August.

1870. Umney (C.). "Nitrite of Amyl." *Pharm. Journ.*, Vol. I., 3rd Ser., p. 422.

1870. Haddon (J.). "Nitrite of Amyl in angina pectoris." *Edin. Med. Journ.*, Vol. XVI., p. 45.

1871. Berger (O.). "Das Amylnitrit, ein neues Palliatiomittel bei Hemicränie." *Allg. med. Centralzeit.* Berlin, May, p. 450.

1871. Brunton (T. L.). "On the action of Nitrite of Amyl on the circulation." *J. Anat. and Physiol.*, Cambr., Vol. V., pp. 92-101.

1871. Jones (T.). "Nitrite of Amyl . . . with suggestions for its employment in cholera." *Practitioner*, Lond., 1871, Vol. VII., pp. 213-234.

1871. Goodhart (J. F.). "Note on the physiological action of Nitrite of Amyl." *Practitioner*, Lond., 1871, Vol. VI., pp. 12-16.

1871. Aldridge. "Account of effects on vessels of retina, and influence of the Nitrites in mental disease." *West Riding Asylum Reports*, Vol. I., 1871.

1871. Gray (St. Clair). "Nitrite of Amyl in Strychnine poisoning." *Glasgow Med. Journ.*, 1871, p. 188.

1871. Wood (H. C.). "Experimental researches on the physiological action of Nitrite of Amyl." Memoir to which was awarded the Warren Prize for 1871 of Massachusetts General Hospital. In *Amer. Journ. Med. Sci.*, Vol. LXII., pp. 39-65, 359.

1872. Hoestermann (C. E.). "Uber die Anwendung des Amylnitrits bei Melancholie." *Wien. med. Woch.*, 1872, Vol. XXII., pp. 1148, 1176, 1201.

1872. Hoffmann (F. A.). "Beitrag zur Kenntniss der physiologischen Wirkungen des salpetrigsauren Amyloxyds." *Arch. f. Anat., Physiol. u. Wissensch. Med.*, Leipz., 1872, pp. 746-753.

1872. Jenks. "Nitrite of Amyl in convulsions after delivery (followed by hæmorrhage)." *Phil. Med. Times*, 1872, Vol. II., p. 404.

1872. Madden (W. H.). "Nitrate (*sic*) of Amyl in angina pectoris." *Practitioner*, Vol. IX., 1872, p. 331. An account by a sufferer from angina of its effects on himself.

1872. von Schroff (C., jun.). "Amyl-nitrit." *Med. Jahr.*, Wien, 1872, pp. 490-493.

1872. Smith (F. P.). "On Nitrite of Amyl." *Practitioner*, Lond., Vol. VIII., p. 61.

1873. Amez-Droz. "Étude sur le nitrite d'amyle." *Arch. de Physiol. Norm. et Path.*, Par., Vol. V., pp. 467-503.

1873. Bernheim. "Ueber die Wirkung des salpetrigsauren Amyl-oxyds." *Arch. f. d. ges. Physiol.* (*Pflüger's Arch.*), Bonn, Vol. VIII., pp. 253-257.

1873. Eulenburg (A.) & Guttmann (P.). "Zur Kenntniss der Wirkung des Amyl-nitrits." *Arch. f. Anat., Physiol. u. Wissensch. Med.*, Leipz., pp. 442-448.

1873-4. Flagg (S.). "Nitrite of Amyl." *Northwest M. and S. Journ.*, St. Paul, Minn., Vol. IV., pp. 52-54.

1873. Kitchen (D. H.). "Nitrite of Amyl in the treatment of spasmodic asthma and acute bronchitis." *Amer. Journ. Insan.*, Vol. XXIX.

1873. Pick (R.). "Ueber das Amyl-nitrit und seine therapeutische Anwendung." *Centralbl. f. d. med. Wissnesch.*, Berl., Vol. XI., pp. 865-867. Also transl. *Cincin. Med. News*, 1874, Vol. III., pp. 387, 393. Also reprint, 1877.

1873. **Steketee** (C.). "Jets over Nitris Amyli." 8vo., Utrecht.

1874. **Browne** (J. C.). "Notes on the Nitrite of Amyl." *Practitioner*, Lond., Vol. XIII., pp. 179-184. Also *Med. Gaz.*, June 11th, 1870.

1874. **Berger** (O.). "Ueber Amyl-nitrit." *Deut. Ztschr. f. prakt. Med.*, Leipz., Vol. I., pp. 395-397.

1874. **Filehne** (W.). "Ueber den Einfluss des Amyl-nitrits auf Gefässtonus und Herzschlag." *Arch. f. d. ges. Physiol. (Pflüger's Arch.)*, Bonn., Vol. IX., pp. 470-491.

1874. **Fuckel.** "Zur therapeutischen Anwendung des Amylnitrits." *Deut. Arch. f. klin. Med.*, Leipz., Vol. XIV., pp. 149-152.

1874. **Janeway** (E. G.). "Action of Nitrite of Amyl in restoring temporarily a moribund patient." *New York Med. Journ.*, Vol. XX., p. 58.

1874. **Ladendorf** (A.). "Ueber das Verhalten der Kopftemperatur bei Amyl-nitrit Inhalationen." *Berl. klin. Woch.*, Vol. XI., pp. 537-539. Abstract in *Schmidt's Jahrbücher*, 1876, Bd. 170, p. 11.

1874. **Labadie-Lagrave.** "Effets physiologiques du nitrite d'amyle." *Gaz. Hebd. de Méd.*, Paris, S. II., Vol. XI., pp. 731-734, 747-749.

1874. **Madden** (W. H.). "Amyl-nitrite." *Practitioner*, Lond., Vol. XII., p. 295.

1874. **Pick** (R.). "Ueber das Amyl-nitrit und seine therapeutische Anwendung." Berlin.

1874. **Schramm** (A.). "Ueber die Wirkungen des Amyl-nitrits inbesondere bei Melancholie." Berlin. Also *Arch. f. Physchiat.* Berl., 1875, Vol. V., pp. 317-340.

1874. **Schüller** (M.). "Ueber die Einwirkung einiger Arzneimittel auf die Gehirngefässe." *Berl. klin. Woch.*, Vol. XI., p. 294; *Med. Times and Gaz.*, 1874, Vol. II., p. 665.

1874. **Veyrières** (F.). "Recherches sur le nitrite d'amyle; action physiologique, effets thérapeutiques." Paris.

1874. **Wood** (H. C., jun.). "Physiological action of the Nitrite of Amyl." *Tr. Coll. Phys.*, Phila. (1871), 1874 (n.s.), Vol. IV., pp. 366-368.

1875. **Bader** (C.). "The Dangers of Chloroform, etc., and the Nitrite of Amyl." *Lancet*, 1875, Vol. I., p. 644.

1875. **Filehne** (W.). "Zur Wirkung des Amyl-nitrits." *Berl. klin. Woch.*, Vol. XII., p. 601.

1875. **Hinton** (R. R.). "Nitrite of Amyl in hysterical convulsions, the cold stage of intermittents, and chloroform-narcosis." *Phila. Med. Times*, Vol. V., p. 694.

1875. Kelp. "Amyl-nitrit." *Deut. Arch. f. klin. Med.*, Leipz., Vol. XV., p. 602.

1875. McBride (J. H.). "Experimental and clinical observations on the use of Nitrite of Amyl in epilepsy." *Chicago Journ. of Nervous and Mental Diseases*, September, 1875.

1875. Marsat (A.). "Des usages thérapeutiques du nitrite d'amyle." Paris.

1875. Mayer (S.). "Ueber die physiologischen Wirkungen des Amyl-nitrit." *Aerztl. Cor.-bl. f. Bôhmen. Prag.*, Vol. III., pp. 53-59.

1875. Minor (J. L.). "On the use of Nitrite of Amyl in various forms of spasm, and on its value as a diagnosis." *Tr. Coll. Phys.*, Phila., Vol. I., 105-120. Also *Phila. Med. Times*, 1874-5, Vol. V., pp. 353-357.

1875. Mayer (S.) & Friedrich (J. J.). "Ueber einige physiologische Wirkungen des Amyl-nitrit." *Arch. f. exper. Path. u. Pharmakol.*, Leipz., Vol. V., pp. 55-85; 2 pl.

1875. Otto (A.). "Ueber Amyl-nitrit." *Allg. Ztschr. f. Physchiat.*, Berlin, Vol. XXXI., pp. 441-462.

1875. Philip (J. A.). *Journ. of Mental Sci.*, January, 1875 (n.s.), Vol. XX., p. 600.

1875. Samelsohn (J.). "Zur Wirkung des Amyl-nitrits." *Deut. Ztschr. f. prakt. Med.*, Leipz., Vol. III., pp. 412-415. Also *Berl. klin. Woch.*, Vol. XII., pp. 332, 349.

1875. Smart (W. N.). "The relations of Nitrite of Amyl to Chloroform." *Detroit Rev. Med. and Pharm.*, Vol. X., pp. 661-666.

1875. Tebaldi (A.). "Del nitrito d'amile. Sua azione . . . . nelle malattie mentali." *Riv. sper. di. freniat.* Reggio Emilia, Vol. I., pp. 177, 281.

1875. Wiglesworth (A.). "On the effects of Nitrite of Amyl." *Lancet*, 1875, Vol. I., p. 743.

1876. Bourneville. "De l'action physiologique du nitrite d'amyle et de son emploie dans le traitement de l'épilepsie." *Mém. Compt. Rend. Soc. de Biol.*, Paris, 6th S., Vol. III., p. 45.

1876. Burrall (F. A.). "Amyl-nitrite as an antidote to Chloroform." *New York Med. Journ.*, Vol. XXIV., p. 467.

1876. Hutchins (A.). "The Nitrite of Amyl." *Proc. Med. Soc., County Kings*, Brooklyn, Vol. I., pp. 35-61.

1876. Jolyet & Regnard (P.). "Note sur les modifications apportées dans les produits de la respiration et sur le sang par les inhalations de nitrite d'amyle." *Compt. Rend. Soc. de Biol.*, Paris, 6. S., Vol. III., pp. 214-218. Also *Gaz. Méd. de Par.*, 1876, p. 340.

1876. Köhler (H.). "Untersuchungen über das Amylnitrit." *Schmidt's Jahrb.*, Bd. 170, p. 10.

1876. Mader. "Ueber die physiologische und therapeutische Wirkung des Amyl-nitrits." *Wien. med. Presse*, Vol. XVII., pp. 1697-1699.

1876. Osgood (H.). "Nitrite of Amyl in Intermittent Fever." *Tr. Coll. Phys. Phila.*, Vol. VI., p. 489.

1876. Pick (R.). "Zur physiologischen und therapeutischen Würdigung des Amyl-nitrits." *Deut. Arch. f. klin. Med.*, Leipz., Vol. XVII., pp. 127-147.

1876. Pick (R.). "Ueber die physiologische Wirkung des Amylnitrits und seinen therapeutischen Werth bei Neurosen u. Psychosen." *Irrenfreund*, Heilbr., Vol. XVIII., pp. 25-33.

1876. Saunders (W. E.). "Nitrite of Amyl in ague, etc." *Indian Med. Gaz.*, Calcutta, Vol. XI., p. 289.

1876. Van Ermengem (E.). "Étude sur le nitrite d'amyle; action physiologique; usages thérapeutiques." Louvain. Also *Journ. de Sci. Méd. de Louvain*, Vol. I., pp. 393, 449, 513, 561.

1876. Verga (C. B.). "Delle malazione di nitrito d'amilo in alcuni frenosi." *Arch. ital. per le mal. nerv.*, Milano, Vol. XIII., pp. 204-211. *Journ. of Mental Science*, January, 1877, p. 629.

1876. Zeigler (C. W.). "On the use of Nitrite of Amyl, especially in chorea." *Phila. Med. Times*, Vol. VI., pp. 486-489.

1877. Bayles (G.). "Nitrite of Amyl in whooping cough." *New York Med. Record*, Vol. XII., p. 410. *Lond. Med. Record*, Vol. V., p. 332.

1877. Burnett (S. M.). "Nitrite of Amyl in Tinnitus Aurium." *New York Med. Record*, Vol. XII., p. 483. Abst. *Practitioner*, 1878, Vol. XX., p. 458.

1877. Griswold (R. M.). "Upon the use of Nitrite of Amyl." *Proc. Connect. Med. Soc.*, Hartford, 1877, 75.

1877. Lane (W. L.). "Some experiments with Nitrite of Amyl." *Brit. Med. Journ.*, 1877, Vol. I., p. 101.

1877. Maximowitsch (J.). "Die therapeutische Andwendung des Amyl-nitrits." *St. Petersb. Med. Woch.*, Vol. II., p. 91.

1877. Urbantschitsch (V.). "Ueber die therapeutische Wirkung des Amyl-nitrits." *Wien. Med. Presse*, Vol. XVIII., pp. 225, 262, 294, 359, 390.

1877. Weber-Liel. "Zur Anwendung des Amyl-nitrits bei Ohrenkrankheiten." *Monatschr. f. Ohrenh.*, Berl., Vol. XI., p. 39.

1878. Burrall (F. A.). "The Nitrite of Amyl as an antidote to Chloroform." *New York Med. Record*, Vol. XIV., p. 43.

1878. Eisenstein. "Use of Nitrate of Amyl in angina pectoris." Abst. *Lond. Med. Record*, Vol. VII., p. 102.

1878. Giacosa (P.). "Sull 'azione del nitrito d'amilo sulla sostanza colorante del sangue." *Arch. per le sci. med.*, Torino, Vol. III., No. 12. See also *Zeit. f. phys. Chem.*, Vol. III., p. 54.

1878. Kiernander (H.). "Nitrite of Amyl in ague." *Lancet*, 1878, Vol. I., pp. 112, 261.

1878. Minor (J. L.). "Amyl-nitrite as a Cardiac Stimulant." *Virginia. Med. Month.*, Richmond, Vol. IV., p. 876. *Practitioner*, Vol. XXI., p. 218.

1878. Price (G.). "Nitrite of Amyl in ague." *Lancet*, 1878, Vol. I., p. 445.

1878. Ralfe. "A case of ague treated with Nitrite of Amyl." *Lancet*, 1878, Vol. II., p. 693.

1878. Saunders (W. E.). "Nitrite of Amyl in ague." *Indian Med. Gaz.*, No. 39. *Practitioner*, Vol. XXI., 218. *Lancet*, 1878, Vol. I., p. 37.

1879. Coghill (J. G. S.). "Nitrite of Amyl in Chloral poisoning." *Brit. Med. Journ.*, 1879, Vol. I., p. 969.

1879. Dingle & Alford. "On Nitrite of Amyl in sea sickness." *Lancet*, 1879, Vol. I., pp. 650, 687.

1879. Dugau (P. H.). "Recherches critiques et expérimentales sur le nitrite d'amyle." Paris. Also quoted in *Lond. Med. Rec.*, 1880, Vol. VIII., p. 313. Also *Rev. Mens. de Méd. et de Chir.*, July, 1880.

1879. Emminghaus. "On Amyl Nitrite in the dyspnœa of consumption." (*Memorab.*, Nov.). Abst. *Lond. Med. Record*, 1880, Vol. VIII., p. 18.

1879. Filehne (W.). "Die Wirkungen des Amyl-nitrits." *Arch. f. Physiol.*, Leipz., 385-416.

1879. François-Franck. "Sur l'action vasculaire comparée des anesthèsiques et du nitrite d'amyle." *Compt. Rend. Soc. d. Biol.*, 7th S., Vol. I., pp. 137-139. Abst. *Lond. Med. Record*, Vol. VII., p. 321. *Progrès Médicale*, May 10th.

1879. Gaspey (O.). "Ueber den Einfluss des Amyl-nitrits auf die Weite der Gefässe in gesunden und kranken Geweben." *Arch. f. path. Anat. etc.*, Berlin, Vol. LXXV., pp. 301-316.

1879. Giacosa (P.). "Ueber die Wirkung des Amyl-nitrits auf das Blut." *Zeit. f. physiol. Chem.*, Strassburg, Vol. III., pp. 54-57.

1879. Hawes. "The internal administration of Nitrite of Amyl." (Cases). *Tr. Detroit Med. and Libr. Ass.*, Vol. I., p. 12.

1879. Hönigschmied (E.). "Erfahrungen über Amyl-nitrit." *Med. Chir. Centralbl.*, Wien, Vol. XIV., p. 423.

1879. Illingworth (C. R.). "Nitrite of Amyl in sea-sickness." *Lancet*, 1879, Vol. II., p. 184.

1879. Kerr (E. W.). "Nitrite of Amyl in uterine hæmorrhage." *Brit. Med. Journ.*, 1879, Vol. II., p. 691.

1879. Maragliano (E.). "Il nitrito d'amile nella cura dell'epilessia." *Salute* (suppl.), Genova, Vol. V., pp. 113-122, 161, 193, 209. Abst. *Pract.*, 1881, Vol. XXVII., p. 57. (Translated by J. Workman, *Alienist and Neurol.*, St. Louis, Vol. II., pp. 20-25.)

1879. Riddell (R.). "Notes on Croton Chloral and Nitrite of Amyl." *Dublin Journ. Med. Sci.* (3rd S.), Vol. LXVII., pp. 346-350.

1879. Sassezki (N.). "Ueber die Wirkung des Amyl-nitrits auf die Körpertemperatur." *St. Petersb. Med. Woch.*, Vol. IV., p. 392.

1879. Smith (W. R.). "Nitrite of Amyl in 'Congestive Chills.'" *Ohio Med. Recorder*, Columbus, Vol. III., p. 346.

1879. Thibaut (D.). "Du nitrite d'amyle." *Bull. Méd. du Nord.*, Lille, Vol. XVIII., pp. 124-131.

1879. Tasitski (P.). "Odieistoii amil-nitrita na temperaturu." *Voyenno Med. Journ.*, St. Petersb., Vol. CXXXV., September, pp. 55-72.

1879. Teixeira de Souza (J. E.). "Da accâo physiologica e therapeutica do nitrito de amylo." *Ann. Brazil de Med.*, Rio de Janeiro, 1879-80, Vol. XXXI., pp. 61-90.

1879. Testa (B.). "Le applicazioni terapiche del nitrito amilico." *Gior. internaz. d. Sci. Med.*, Napoli, (n.s.), Vol. I., pp. 535-541.

1879. von Eisenstein (R.). "Versuche mit Amyl-nitrit und Tct. Gelsemii." *Med. Chir. Centralbl.*, Wien., Vol. XIV., p. 183.

1880. Burke (J.). "Chloroform narcosis and Nitrite of Amyl." *New York Med. Record*, Vol. XVII., p. 219.

1880. Keating (J. M.). "Internal administration of Nitrite of Amyl as a stimulant in the typhoid state." *Phila. Med. Times*, 1880-1, Vol. XI., p. 167.

1880. McCullough (J.). "On Nitrite of Amyl as an antidote in Chloral poisoning." *Canada Lancet*, 1879-80, Vol. XII., p. 73. Abst. *Lond. Med. Record*, Vol. VIII., p. 52.

1880. Ozil (Paul François Stanislaus). "Étude bibliographique et clinique du nitrite d'amyle." Lille, p. 162.

1880. Ceuter (G. F.)." Poisoning by Nitrite of Amyl." *Indiana Med. Reporter*, Evansville, Vol. 1., p. 70.

1880. Reed (R. H.). "Nitrite of Amyl; its history, physiological action, and therapeutics." *Detroit Lancet*, 1879-80, Vol. III., pp. 337-344.

1880. Weiser. "Action of Nitrite of Amyl on the urine, and its use in the treatment of chronic vesical catarrh." *Med. Chir. Rundeschau*, March. *Lyon Méd.*, December 19th, 1880. Abst. *Practitioner*, 1880, Vol. XXV., p. 60; 1881, XXVI., p. 380.

1881. Alexander. "Ischæmia Retinæ; Heilung durch Amylnitrit." *Deut. med. Woch.*, Berlin., Vol. VII., p. 548.

1881. Atkinson (F. P.). "The relief of toothache by the application of Nitrite of Amyl and Nitro-glycerine." *Practitioner*, Lond., Vol. XXVII., p. 265.

1881. Littlefield (J. Dana). "Nitrite of Amyl in tinnitis aurium." *Amer. Med. and Surg. Reporter*, Nov. 26th. *Practitioner*, Lond., 1882, Vol. XXVIII., p. 378.

1881. Gibson (C.). "On Sea-sickness." *Brit. Med. Journ.*, 1881, Vol. II., p. 730.

1881. Kulz. "Administration of Nitrite of Amyl in fatty degeneration of the heart." *Riv. clin. di Bologna*, January, 1881. Abst. *Practitioner*, Vol. XXVIII., p. 378.

1881. Kurz (E.). "Zur Anwendung des Amyl-nitrit." *Memorabilien*, Heilbr., n.f., Vol. I., pp. 65-73.

1881. Michael (J.). "Employment of Nitrite of Amyl in diseases of the ear." *Ann. des Mal. de l'oreille, &c.*, March. Abst. *Lond. Med. Record*, Vol. IX., p. 431.

1881 Reichert (Edward T.). "Amyl Nitrite, a powerful cardiac stimulant." *New York Med. Journ.*, Vol. XXXIV., p. 33.

1881. Samelsohn (J.). "Zur ophthalmo-therapeutischen Wirkung des Amyl-nitrits." *Centralbl. f. prakt. Augenh.*, Vol. V., p. 200. Abst. *Lond. Med. Record*, Vol. IX., p. 471.

1881. Sheather (C.). "Nitrite of Amyl." *Vet. Journ. and Ann. Comp. Path.*, Lond., Vol. XII., pp. 182-186.

1881. Turnbull (C. S.). "Amyl-nitrite in tinnitus aurium." *Med. and Surg. Reporter*, Phila., Vol. XLV., p. 669.

1881. Turner (E. F.). "Amyl-nitrite in Opium poisoning." *St. Louis Cour. Med.*, Vol. VI., p. 304.

1882. Bridger (A. E.). "Nitrite of Amyl in the infantile convulsions of children." *Lancet*, 1882, Vol. I., p. 667.

1882. Fox (C. J.). "Syncope with cerebral disturbances fully relieved by the use of the Nitrite of Amyl." *N. Eng. Med. Month.*, Newtown, Conn., Vol. II., p. 399.

1882. Ross (G. W. H.). "Amyl-nitrite in tetanus; a case." *Mich. Med. News*, Detroit, Vol. V., p. 90.

1882. Testa. "Alleged antagonism between Nitrite of Amyl and Chloroform." *Gaz. Med. Ital., Prov. Ven.*, October 29th and November 5th, 1881. Abst. *Lond. Med. Record*, 1882, Vol. X., p. 73.

1882. Thompson (W. H.). "Singultus treated by Nitrite of Amyl." *New York Med. Rec.*, Vol. XXII., p. 231.

1882. Williams (J.). "Spasm of glottis treated by Nitrite of Amyl." *Canada Med. and Surg. Journ.*, September. Abst *Practitioner*, Vol. XXIX., p. 446.

1883. Anhona (D.). "Use of Nitrite of Amyl in febrile diseases of the respiratory organs." *Therapeutic Gaz.*, November, 1883. *Ed. Med. Journ.*, Vol. XXIX., p. 654.

1883. D'Ancona (N.). "Il nitrito d'amile." *Gaz. Med. Ital., Prov. Venet.*, Pad., Vol. XXVI., 33-37.

1883. Fox (C. J.). "Nitrite of Amyl." *N. Eng. Med. Month.*, Sandy Hook, Conn., 1883-4, Vol. III., p. 507.

1883. Ringwood. "Nitrite of Amyl in uræmic asthma." *Brit. Med. Journ.*, 1883, Vol. I., p. 1064. Abst. *Lond. Med. Record*, 1883, Vol. II., p. 321.

1883. Smith (S. C.). "On Nitrite of Amyl in uræmic asthma." *Brit. Med. Journ.*, 1883, Vol. I., p. 1115. Abst. *Lond. Med. Record*, Vol. XI., p. 321.

1883. Steele (N. C.). "Nitrite of Amyl in hour-glass contraction." *Mississippi Valley Med. Month.*, Memphis, Vol. III., p. 247.

1883. Sheen (A.). "Nitrite of Amyl and Nitro-glycerine in uræmic asthma." *Brit. Med. Journ.*, 1883, Vol. I., p. 811.

1883. De Renzi (E.). "Inalazioni di nitrito di amile." *Riv. Clin. e Terap. Napoli*, Vol. V., pp. 1-13.

1883. Testa (B.). "Nitrito amilico e nitro-glicerina." *Indip.* Torino, Vol. XXXIV., pp. 433, 457.

1883. Tosoni. "Contribuzione alla terapia della corea." *Ann. univ. di med. e chir.*, No. 7. Abst. *Centralbl. f. klin. Med.*, Leipz., 1884, p. 328.

1884. Alt (A.). "On tinnitis aurium and the therapeutic value of Nitrite of Amyl in this affection." *Weekly Med. Rev.*, Chicago, Vol. X., pp. 92-99.

1884. Dittel. "Nitrite of Amyl for ammoniacal urine." *Allg. Wien. Med. Zeit.*, Jan., 1884. Abst. *Pract.*, Vol. XXXIII., p. 213.

1884. Dixon (J. F.). "On the internal use of Nitrite of Amyl." *Brit. Med. Journ.*, 1884, Vol. II., p. 147.

1884. Hayem. "Amyl-nitrite." *Compt. Rend. d'Acad. des Sci.*, pp. 580-583.

1884. Hare (H. A.). "The Nitrite of Amyl as an antidote in Strychnia poisoning." *Boston Med. and Surg. Journ.*, Vol. CXI., p. 481. Abst. *Lond. Med. Record*, 1885, Vol. XIII., p. 75.

1884. Richardson (B. W.). "Internal administration of Amyl-nitrite." *Asclepiad*, Lond., Vol. I., p. 165. Also Abst. *Lond. Med. Record*, Vol. XII., p. 294.

1884. Strahan (S. A. K.). "Hypodermic injection of Nitrite of Amyl for lumbago followed by epileptiform convulsions." *Journ. Ment. Sci.*, Lond. (n.s.), Vol. XXX., p. 252. Also Abst. *Lond. Med. Record*, Vol. XII., p. 356.

1885. Macdonald (A. D.). "Nitrite of Amyl as an eliminator of uric acid; a remedy (?) for gout." *Med. Press and Circ.*, Lond. (n.s.), Vol. XL., p. 329.

1885. Macdonald (A. D.). "Nitrite of Amyl as an eliminator of uric acid; its employment in the treatment of gout." *Brit. Med. Journ.*, 1885, Vol. I., p. 1039. Abst. *Lond. Med. Record*, Vol. XIII., p. 284.

1885. Mya (G.). "Influenza delle inalazioni di nitrito d'amilo sulla reazione dell 'urina umana normale e pathologica." *Gaz. d. Clin.*, Torino, Vol. XXI., 49-51.

1885. Lewis (M.). "The use of Amyl-nitrite in the severe paroxysms of whooping-cough." *Polyclinic*, Phila., Vol. III., p. 176. *Therap. Gaz.*, Detroit, 1886 (3rd S.), Vol. II., p. 231.

1886. Lahnstein (F.). "Die Beeinflussung unserer Haut-temperatur durch Amyl-nitrit." *Diss.*

1886. Török (G.). "Idült Mérgezés Amyl-nitrittel." (Chronic poisoning by Amyl-nitrite). *Orvosi Hetil.*, Buda-pest, Vol. XXX., pp. 1113-1442.

1886. Walter (P. A.). "Effect of Nitrite of Amyl on uric acid." *Vrach.* St. Petersb., Vol. VII., pp. 214-217.

1887. Allman (J. D.). "Physiological and therapeutical notes on Nitrite of Amyl." *Vet. Journ. and Ann. Comp. Path.*, Lond., Vol. V., pp. 95-98.

1887. Dobinski (W.). "Therap. of Nitrite of Amyl." *Pam. Towarz. lek. Warszaw*, Vol. LXXIII., pp. 237-277.

1887. Palm (T. A.). "Nitrite of Amyl in cholera." *Brit. Med. Journ.*, 1887, Vol. II., p. 992.

1888. Bitter (Hendrick, jun.). "Experimenteele onderzoekingen over bestrijding van cocaine vergiftiging door inademing van Amyl-nitriet." (Amsterdam.)

1888. Roesen (J.). "Ueber Vergiftung durch Amyl-nitrit." *Centralbl. f. klin. Med.*, Leipz., Vol. IX., pp. 777-780.

1890. Richardson (B. W.). "On the physiological properties of Nitrite of Amyl." *Asclepiad*, Lond., Vol. VII., p. 178.

1891. Mammen (E.). "Nitrite of Amyl in Chloroform poisoning." *New York Med. Rec.*, Vol. XXXIX., p. 483.

1892. Brunton (T. L.) & Bokenham (T. J.). "On the comparative action of Bertoni's Ether (Tertiary Amyl-nitrite), Amyl-nitrite, and Isobutyl-nitrite." *St. Barth. Hosp. Rep.*, Lond., Vol. XXVIII., pp. 281-287.

1893. Shoemaker (G. E.). "Recovery after swallowing a teaspoonful of Amyl-nitrite." *Med. News*, Phila., Vol. LXII., p. 544.

NITRO-GLYCERINE.

(DYNAMITE, TRINITRINE, GLONOIN.)

1847. Sobrero (Ascagno). "Uber mehrere Knallverbindungen, erhalten durch Einwirkung von Saltpetersäure auf Zucker, Dextrin, Milchzucker, Mannit u. Glycerin." *Compt. Rend.*, Vol. XXIV., p. 147.

1853. Hering (Constantin). "Glonoin oder Nitro-glycerin." *Amerikanische Arzneiprufungen und Vorarbeiten zur Arzneilehre als Naturwissenschaft*, Heft. 1 & 2, Leipz., pp. 129, 140.

1854. Kofler (L.). "Das Glonoin oder Nitro-glycerin. Zugleich als Probe homöopatischer Charlatanerie." *Wittsteins Vjhrschr f. prakt. Pharm.*, Vol. III. 2, p. 225.

1855. de Vrij (J. F.). "Glonoin oder Nitro-Glycerin." *Tijdsch. f. wetensch. Pharm.* 2. Jaarg., No. 3, p. 65.

1855. Pelikan (E.). "Toxicologisches über das Nitro-glycerin (Glonoin) und andere Knallkörper." St. Petersb., *Med. Ztg. Russlands,* St. Petersb., 1855, Vol. XII., pp. 377, 385. *Schmidt's Jahrb.,* Bd. 134, p. 344.

1858. Field (A. G.). "Toxical and medicinal properties of nitrate of oxyde of Glycyl." *Med. Times and Gaz.,* 1858, Vol. I., p. 291.

1858. Fuller & Harley. "Nitro-glycerine, Glonoin." *Med. Times and Gaz.,* 1858, Vol. I., p. 356.

1858. Thorowgood & James. "Glonoin." *Med. Times and Gaz.,* 1858, Vol. I., p. 331.

1859. Field (A. G.). "Nitro-glycerine or Glonoin." *Med. Times and Gaz.,* 1859, Vol. I., p. 339.

1859. Brady (G. S.). "On the medicinal action of Glonoin." *Med. Times and Gaz.,* 1859, Vol. I., p. 263.

1859. Baker Edwards. "On the physiological actions of Xyloids." *Liverpool Med. Chir. Journ.,* Jan. 2nd.

1859. Vulpian. "De l'emploi thérapeutique de la glonoine et de la nitro-glycérine." *Gaz. Hebd. d. Med. et Chir.,* March 6th.

1859. Demme (R.). "Das Nitro-glycerin. als Arzneimittel." *Schweiz. Ztschr. f. Heilk.,* Vol. I., p. 156. *Buchner's Rep. f. Pharm.,* Vol. XII., p. 431.

1859. Merrick (John). "Uber die Schädlichkeit einer Inhalation von Nitro-glycerin." *Silliman's Amer. Journ.,* Vol. XXXVI., No. 107, p. 212.

1864. Albers (J. F. H.). "Uber die physiolog. u. therapeutische Wirkung des Nitro-glycerins." *Deut. Klin.,* 42, *Schmidt's Jahr.,* Bd. 125, p. 54.

1865. Eulenberg (H.). "Uber die Wirkung des Nitro-glycerins." *Berl. klin. Woch.,* Vol. II., 24; *Schmidt's Jahr.,* Bd. 128, p. 289.

1866. Werber (A.). "Beitrag zur Kenntniss des toxikologischen Wirkung des Nitro-glycerin." *Deut. Klin.,* 49.

1866-7. Nyström (C.). "On the toxicology of Nitro-glycerine." *Upsala Läkareforenings Förhandlingar,* Bd. II., No. 4, p. 232.

1867. Honert. "Ein Fall von Vergiftumg durch Nitro-glycerin." *Deut. Klin.,* 9.

1867. Husemann (T.). "Das Nitro-glycerin in toxokologischer und therapeutischer Bedeutung." *Schmidt's Jahrb.,* Bd. 134, p. 344.

1872. Holst (J. C.). "Case of Nitro-glycerine poisoning." *Schmidt's Jahrb.,* Bd. 154, p. 271. *Norsk Mag.,* XXIV., 10, p. 541, 1870.

1875. Douglas-Lithgow (R. A.). "Nitrite of Amyl in nervous cephalalgia." *Lancet*, 1875, Vol. II., p. 556.

1876. Bruel. "Recherches expérimentales sur les effets toxiques de la nitro-glycerine et de la dynamite." Paris.

1876. Brunton & Tait. "Physiological action of Nitro-glycerine." *St. Barth. Hosp. Rep.*, p. 140.

1879. Jameson (G.). "Nitro-glycerine in angina pectoris." *Lancet*, 1879, Vol. I., p. 578.

1879. Murrell (W.). "Nitro-glycerine as a remedy for angina pectoris." *Lancet*, 1879, Vol. I., pp. 80, 113, 151, 225.

1880. Martindale (W.). "Nitro-glycerine in pharmacy." *Brit. Med. Journ.*, 1880, Vol. I., pp. 406, 487. Also *Practitioner*, Vol. XXIV., p. 35.

1880. Robson (Mayo). "On the use of Nitro-glycerine." *Brit. Med. Journ.*, 1880, Vol. I., p. 556. *Lond. Med. Rec.*, Vol. VIII., p. 187.

1880. Robson (Mayo). "The use of Nitro-glycerine in acute and chronic Bright's disease and in the vascular tension of the aged." *Brit. Med. Journ.*, 1880, Vol. II., p. 803.

1880. Falk. *Lehrbuch der practischen Toxicologie*, p. 191.

1880. Catilena. "Angine de poitrine. Inutilité de la nitro-glycerine." *Sperimentale*, April, p. 348.

1881. Anderson (McC.). "Cases illustrative of the influence of Nitro-glycerine in angina pectoris and of Casca in dilatation of the heart." *Glasgow Med. Journ.*, (n.s.), Vol. XVI., pp. 33-37.

1881. Butterfield. "On the purgative effects of Nitro-glycerine." *Therap. Gaz.*, March.

1881-2. Hammond (W. A.). "Some of the therapeutical uses of Nitro-glycerine." *Virginia Med. Month.*, Richmond, Vol. VIII., pp. 525-531. Also *Lond. Med. Rec.*, 1882, Vol. X., p. 11.

1881. Korczynski. "Physiological effects of Nitro-glycerine." *Pam. Towarz. Lek. Warszaw*, Vol. LXXVII., pp. 609-628. *Wien. Med. Woch.*, Vol. XXXII., pp. 154-156.

1881. Sawyer (J.). "Nitro-glycerine in the treatment of angina pectoris." *Practitioner*, Lond., Vol. XXVI., p. 41.

1882. Green (W. E.). "Nitro-glycerine in puerperal convulsions." *Brit. Med. Journ.*, 1882, Vol. I., p. 573.

1882. Green (W. E.). "Notes on the use of Nitro-glycerine in the treatment of heart disease." *Practitioner*, Vol. XXVIII., pp. 103-111.

1882. Marsil (D.). " De l'emploi de la nitro-glycerine dans le traitement de l'asystolie." *Union Med. du Canada*, Montreal, Vol. XI., pp. 417-420.

1882. Murrell (W.). " Nitro-glycerine as a remedy for angina pectoris." London.

1882. Nevitt (R. B.). " Toxic effects of Nitro-glycerine." *Canada Journ. Med. Sci.*, Toronto, Vol. VII., p. 45.

1882. Stewart. *Therap. Gaz.*, January and May.

1882. Stilts. *The Gazette.* See also *Therap. Gaz.*, 1882 ; *Boston Med. and Surg. Journ.*, October ; and *Med. News*, April 15th, 1882.

1882. Hamilton (A. McL.). " Nitro-glycerine as a remedy." *Med. News*, Phila., Vol. XL., p. 475.

1882. Root (P. S.). " Nitro-glycerine." *Detroit Clinic*, Vol. I., pp. 407-409.

1883. Bourru. " Sur les propriétés toxiques de la nitro-glycérine." *Bull. Gén. de Thérap.*, Paris, Vol. CIV., pp. 455-457.

1883. Desrosiers (H. E.). " De l'action physiologique et thérapeutique de la nitro-glycerine." *Union Méd. du Canada*, Montreal, Vol. XII., pp. 106-108 ; also p. 153.

1883. Hay (M.). " The chemical nature and physiological action of Nitro-glycerine." *Practitioner*, Lond., Vol. XXX., pp. 422-433.

1883. Huchard (H.). " Propriétés physiologiques et thérapeutiques de la trinitrine." *Bull. Gén. de Thérap.*, April 30th.

1883. Huchard (H.). " Des angines de poitrine." *Revue de Méd.*, Paris, Vol. III., p. 676.

1883. Marieux (L.). " Recherches sur les propriétés physiologiques et thérapeutiques de la trinitre." Paris.

1883. " Medicus." " The subcutaneous injection of Nitro-glycerine." *Med. Times and Gaz.*, Lond., 1883, Vol. I., p. 444.

1883. Sheen (A.). " Nitrite of Amyl and Nitro-glycerine in uræmic asthma." *Brit. Med. Journ.*, 1883, Vol. I., p. 811. Also *Union Med.*, Vol. II., p. 80.

1883. Stockton (C. G.). " Some uses of Nitro-glycerine." *Buffalo Med. and Surg. Journ.*, Vol. XXIII., pp. 337-346.

1883. Testa (B.). " Nitrito amilico e nitro-glycerina." *Indip.* Torino, Vol. XXXIV., pp. 433, 457.

1883. West (C.). " Ein Beitrag zur Kenntniss des Nitro-

glycerin." *Med. Chir., Cor. Bl. f. Deut. Am. Aerzte* Buffalo, Vol. I., No. 2, pp. 6-8.

1884. **Bartholow** (R.). "Nitro-glycerine and the chloride of gold and sodium in the treatment of albuminuria." *Boston Med. and Surg. Journ.*, Vol. CX., p. 32. Also *Maryland Med. Journ.*, Balt., 1883-4, Vol. X., p. 627.

1884. **Bramwell** (J. P.). "Case of epileptiform tic cured by Nitro-glycerine." *Brit. Med. Journ.*, 1884, Vol. II., p. 609.

1884. **Dujardin-Beaumetz.** "Des nouvelles médications cardiaques." *Bull. Gén. d. Thérap.*, Vol. CIV., p. 108.

1884. **Éloy** (C.). "Les propriétés et les usages thérapeutiques de la trinitrine." *Union Méd.*, Paris, 3rd S., Vol. XXXVIII., pp. 49-51.

1884. **Éloy.** "Dynamite." *Dict. Encycl. d. Sci. Med.*, Paris, 1st S., Vol. XXX., pp. 745-756.

1884. **Hay** (M.). "Ueber die Wirkung der Nitrite et des Nitroglycerin bei Angina Pectoris." *Deut. Med. Woch.*, Berlin, Vol. X., p. 441.

1884. **Tambroney** (R.). "Sull' azoine fisiologica e terapeutica della trinitrina e della piscidia eritrina." *Riv. Sper. d. Freniat.* Reggio-Emilia, Vol. X., pp. 333-337.

1885. **Burroughs** (J. B.). "Nitro-glycerine as a substitute for alcoholic remedies." *Therap. Gaz.*, Detroit, 3rd S., Vol. I., p. 450.

1885. **Burzhinski** (P. B.). "The action of Nitro-glycerine on nephritis." (Trans. f. *Vrach.* St. Petersb., Vol. VI., p. 335, by T. Maxwell.) *Practitioner*, Lond., Vol. XXXV., pp. 167-170.

1885. **Deahofe** (S. P.). "Successful treatment of a case of trigeminal neuralgia with Nitro-glycerine." *Med. News*, Phila., Vol. XLVI., p. 208.

1885. **Lublinski** (W.). "Ueber die therapeutische Wirksamkeit des Natrium-nitrits u. des Nitro-glycerins." *Deut. Med. Woch.*, Vol. XI., pp. 65, 85.

1885. **Lentovski** (S.). "Effect of Nitro-glycerine upon the albumen in nephritis." *Med. pribav. k. morsk. Sbornkiu.*, St. Petersb., September, pp. 188-203.

1885. **Schultz** (O. T.). "Case of obstinate hiccough relieved by Nitro-glycerine." *Amer. Pract.*, Louisville, Vol. XXXII., p. 161.

1886. **Foy** (G. M.). "Nitro-glycerine." *Med. Press and Circ.* Lond. (N.S.), Vol. XLI., p. 6.

1886. Gordon (W. S.). "Nitro-glycerine as a therapeutic agent." *Practice*, Richmond, 1886-7, Vol. I., pp. 26-28.

1886. Hammond (W. A.). "Glonoin in Migraine or Sick Headache." *Med. Brief.*, St. Louis, Vol. XIV., pp. 330-332.

1886. von Holst (L.). "Nitro-glycerin bei Herz und Neurenleiden." *St. Petersb. med. Woch.* (n.f.), Vol. III., p. 299, 307.

1886. Kinnicutt (F. P.). "The use of Nitro-glycerine in different forms of nephritis." *New York Med. Journ.*, Vol. XLIII., p. 219.

1886. Kinnicutt (F.). "Nitro-glycerine in the treatment of chronic nephritis." *New York Med. Rec.*, Vol. XXIX., pp. 437-441.

1886. Lentovski (S. A.). "Effect of Nitro-glycerine on albumen in nephritis." *Med. pribav., k. morsk. Sbornkiu*, St. Petersb., pp. 333-343.

1887. Atkinson (G. A.). "The pharmacology of the Nitrites and of Nitro-glycerine." *Trans. Internat. Med. Cong.*, IX., Wash., Vol. III., pp. 57-63.

1887. Crook (J. R.). "Remarks on Nitro-glycerine, with special reference to its application in cardiac diseases." *Post Graduate*, New York, 1887-8, Vol. III., pp. 91-99.

1887. Jennings (O.). "Sur l'arrêt (inhibition) du besoin de la morphine par la nitro-glycerine associée à la sparteine." *Tribune Méd.*, Paris, Vol. XIX., pp. 303-308.

1887. Noer (J.). "Poisonous symptoms from Nitro-glycerine." *Therap. Gaz.*, Detroit, 3rd S., Vol. III., p. 459.

1887. Jumont. "Indications et modes d'emploi de la nitro-glycerine." *France Méd.*, Paris, Vol. I., pp. 269-271.

1887. Trusevitch (J. I.). "Application and doses of Nitro-glycerine." *Méd. Obozr.*, Mosk., Vol. XXVII., pp. 60-67. *St. Petersb. med. Woch.* (n.f.), Vol. IV., pp. 2-5.

1887. Trusevitch (J. I.). "Effect of Nitro-glycerine on the health of man." *Ejened. klin. Gaz.*, St. Petersb., Vol. VII., pp. 198, 213.

1887. Trusevitch (J. I.). "Theory of effect of Nitro-glycerine on different forms of cephalalgia." *Ejened. klin. Gaz.*, St. Petersb., Vol. VII., pp. 523, 542, 565. *Allg. med. Centr.-Ztg.*, Berlin, Vol. LVI., pp. 321, 337, 353.

1887. Trusevitch (J. I.). "Nitro-glycerine in medicine. Materials to study its effect in health and diseases of soldiers." St. Petersb., 317 pp., 8vo.

1887. Lautenbach (L. J.). "The Value of Nitro-glycerine in tinnitus aurium." *Trans. Internat. Med. Cong.*, IX., Wash., Vol. III., p. 875.

1887-8. Atkinson (G. A.). "The Pharmacology of the Nitrites and Nitro-glycerine." *Journ. Anat. and Physiol.*, Lond., Vol. XXII., pp. 225-239, 351-371.

1887-8. Kennedy (R. A.). "Report of a case of diabetes mellitus successfully treated by Nitro-glycerine." *Canada Med. Record*, Montreal, Vol. XVI., pp. 73-79.

1888. Lackersteen (M. H.). "Nitro-glycerine (Glonoin) in collapse." *Med. Standard*, Chicago, Vol. III., p. 131.

1888-9. Bowcock (R. L.). "The history of a case of angina pectoris treated with Nitro-glycerine." *Alabama Med. and Surg. Age*, Anniston, Vol. I., p. 14.

1888-9. Kloman (W. C.). "A suggestion of a new use for Nitro-glycerine." *Maryland Med. Journ.*, Balt., Vol. XX., p. 133.

1888-9. Stewart (D. D.). "Remarkable tolerance of Nitro-glycerine." *Polyclinic*, Phila., Vol. VI., pp. 43, 171.

1889. Burroughs (J. B.). "Nitro-glycerine; a substitute for alcohol in cases of emergency." *Lancet*, 1889. Vol. I., pp. 1238, 1297.

1890-1. Aulde (J.). "Nitro-glycerine. Notes on some new remedies." New York.

1890. Kloman (W. C.). "Nitro-glycerine in gas poisoning." *New York Med. Journ.*, Vol. LII., p. 20.

1890. Lansing (R. R.). "Nitro-glycerine in epileptic seizures." *Physician and Surg.*, Ann Arbor and Detroit, Vol. XII., pp. 536-538.

1890-1. Trimble (J. R.). "Use of Nitro-glycerine in a case of poisoning by carbonic oxide gas." *Maryland Med. Journ.*, Balt., Vol. XXIV., pp. 491-494.

1890-1. Upshur (J. N.). "Practical remarks on Nitro-glycerine and Nitrite of Amyl." *Virginia Med. Month.*, Richmond, Vol. XVII., pp. 875-883.

1891-2. Cates (B. B.). "Nitro-glycerine in the treatment of Raynaud's Disease," with report of a case. *Univ. Med. Mag.*, Phila., Vol. IV., pp. 347-352.

1892. Abramoff (A. D.). "Treatment of croup by Nitro-glycerine." *Med. Pribav. k. Morsk. Sbornkiu*, St. Petersb., Vol. II., pp. 256-258.

1893. Ashton T. G.). "The use of Nitro-glycerine in arteriosclerosis." *Therap. Gaz.*, Detroit, 3rd S., Vol. IX., pp. 736-738.

1893. Himmelsbach (G. A.). "Large doses of Nitro-glycerine." *Med. News*, Phila., Vol. LXII., p. 14.

1893. Humphreys (R.). "Nitro-glycerine in vomiting." *Brit. Med. Journ.*, 1893, Vol. I., p. 693.

1893. Reading (G. E.). "A case of unusual acquired tolerance to Nitro-glycerine." *Therap. Gaz.*, Detroit, 3rd S., Vol. IX., p. 292.

1893. Stewart (D. D.). "Tolerance to Nitro-glycerine easily acquired: limitations of use of the drug in chronic nephritis." *Therap. Gaz.*, Detroit, 3rd S., Vol. IX., pp. 604-606.

1894. Griswold (E.). "A case of singultus treated successfully with Nitro-glycerine." *Journ. Amer. Med. Assn.*, Chicago, Vol. XXIII., p. 643.

PLATES.

PLATE I.

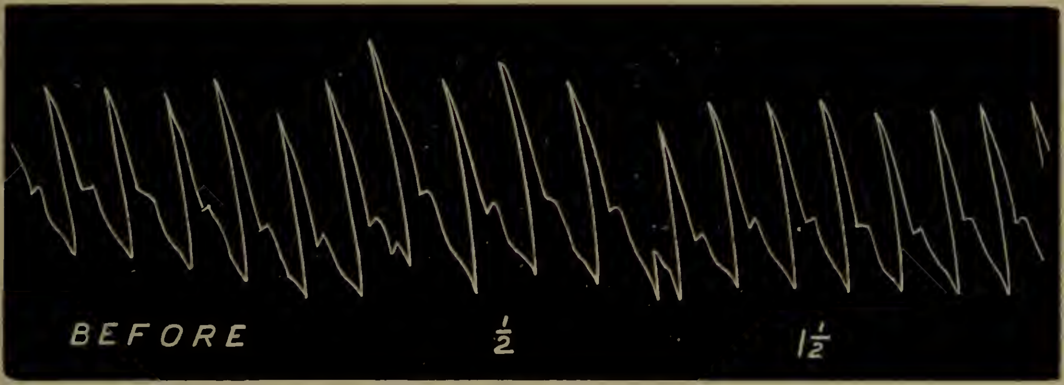


FIG. 1.—Tracing of pulse from V. C. before, and ½ and 1½ minutes after, the administration of 100 minims of spirit of nitrous ether.

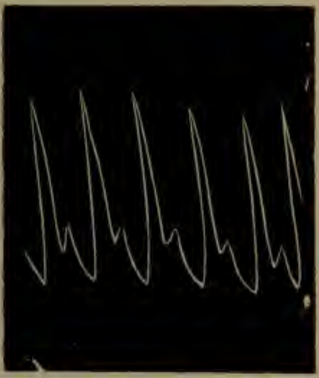


FIG. 2.—Tracing taken 3 minutes after administration of the dose of ℳ100 of spirit of nitrous ether.

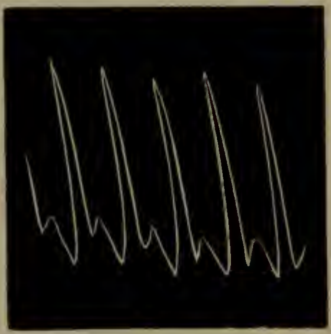


FIG. 3.—Tracing taken 8 minutes after the dose.

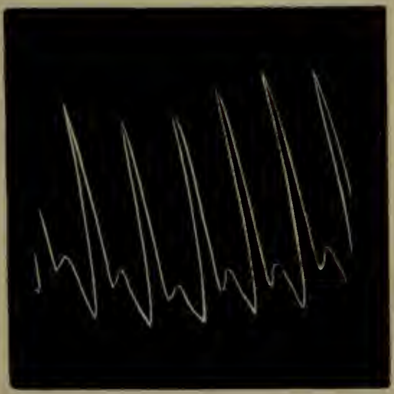


FIG. 4.—Tracing 30 minutes after the dose.

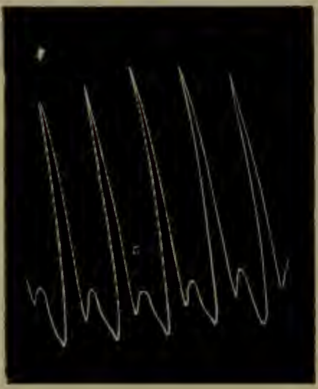


FIG. 5.—60 minutes after the dose.

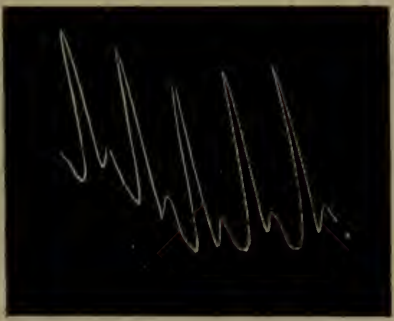


FIG. 6.—80 minutes after the dose.

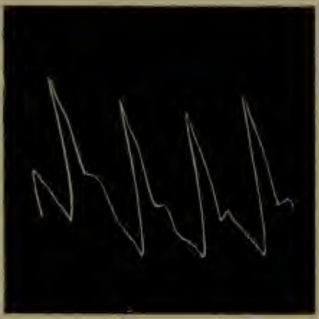


FIG. 7.—3¾ hours after the dose.

PLATE II.

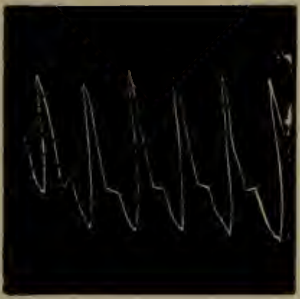


FIG. 8.—Tracing of pulse before the administration of 50 minims of spirit of nitrous ether. From V.C.

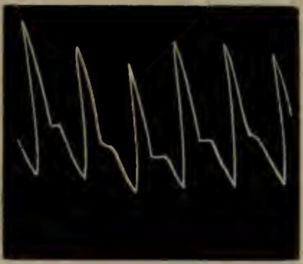


FIG 9.—10 minutes after the dose.

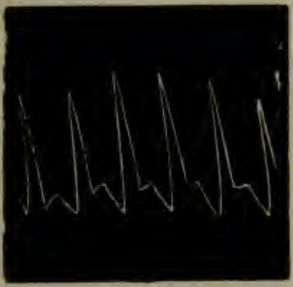


FIG. 10.—30 minutes after the dose.

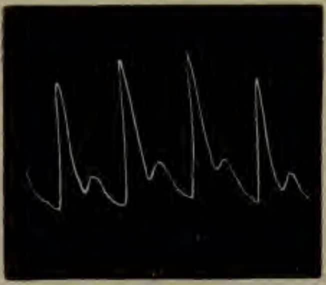


FIG. 11.—One hour after the dose.

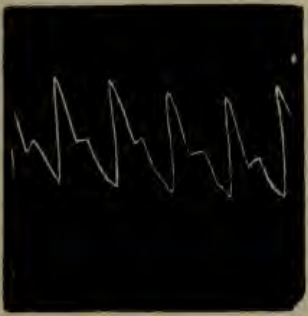


FIG. 12.—Before administration of 25 minims. From V. C.

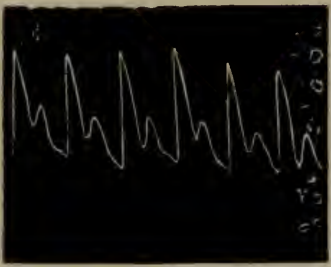


FIG. 13.—8 minutes after the dose.

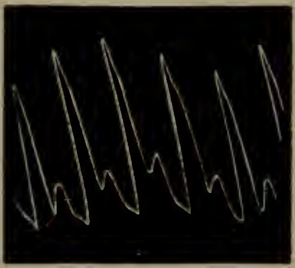


FIG. 14.—50 minutes after the dose.

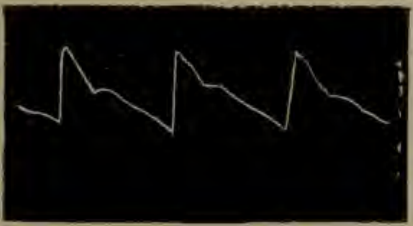


FIG. 15.—Before m100 of spt. æth. nitr. From Mr. E.

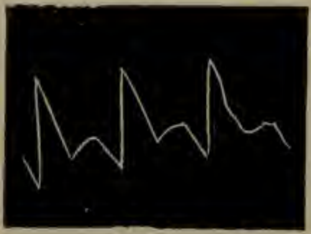


FIG. 16.—8 minutes after.

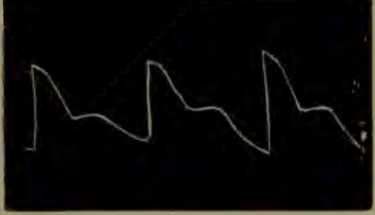


FIG. 17.—35 minutes after.

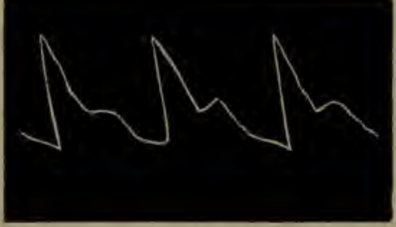


FIG. 18.—60 minutes after.

PLATE III.

Amyl Nitrite.

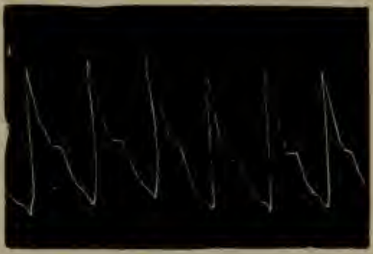


FIG. 19.—Normal.

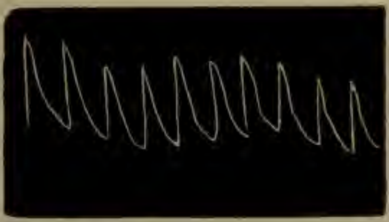


FIG. 20.—15 seconds.

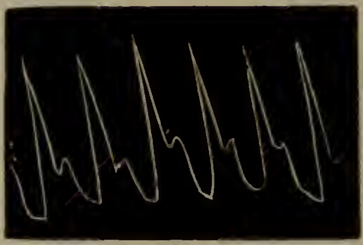


FIG. 21.—75 seconds.

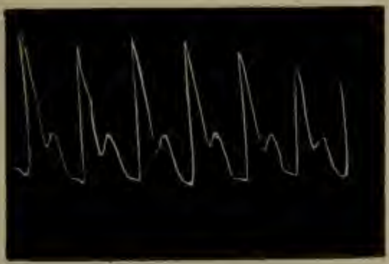


FIG. 22.—11 minutes.

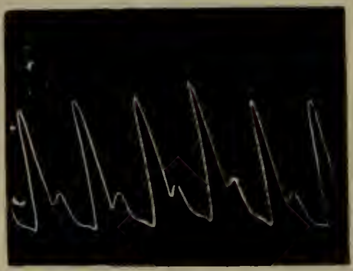


FIG. 23.—23 minutes.

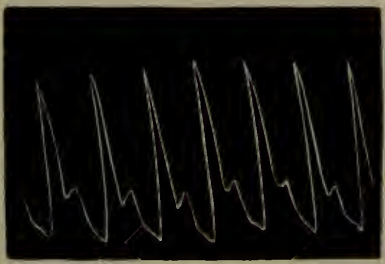


FIG. 24.—60 minutes.

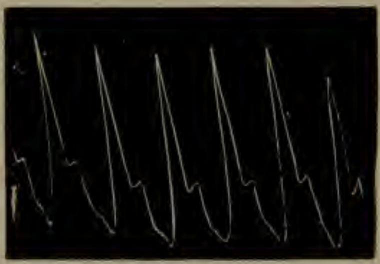


FIG. 25.—74 minutes.

PLATE IV.

Ethyl Nitrite, ♏ xxv.

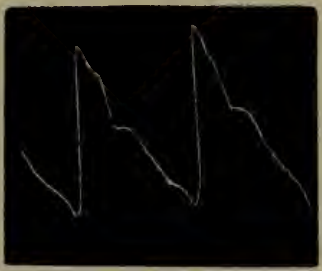


Fig. 26.—Normal.

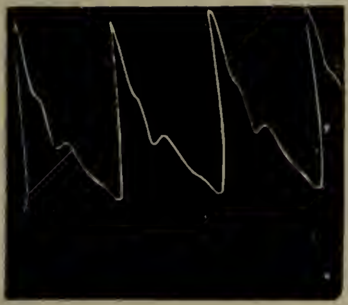


Fig 27.—4 minutes.

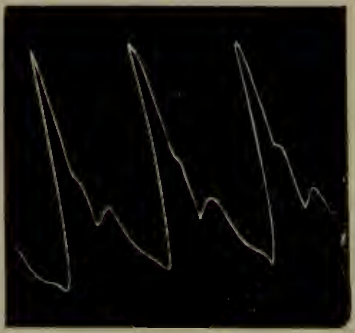


Fig. 28.—12 minutes.

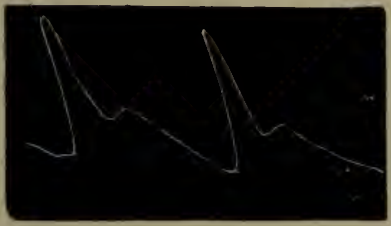


Fig. 29.—32 minutes.

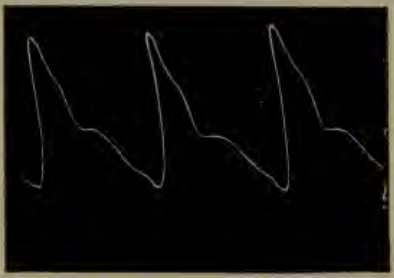


Fig. 30.—50 minutes.

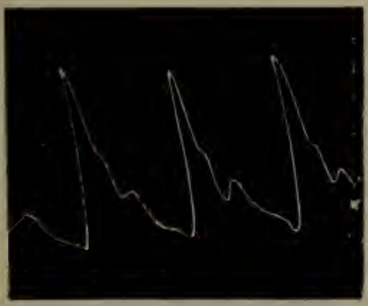


Fig. 31.—1 hour 30 minutes.

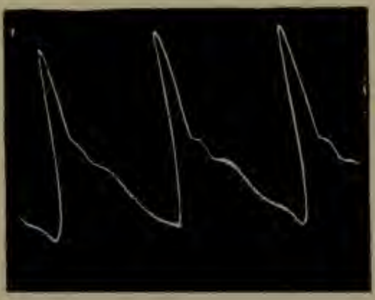


Fig. 32.—1 hour 50 minutes.

PLATE V.

Ethyl Nitrite, ♏ xxv.

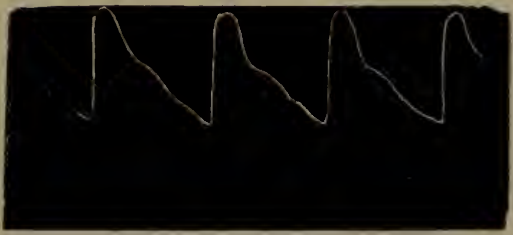


FIG. 33.—Normal.

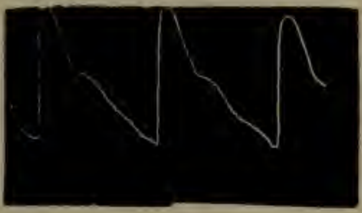


FIG. 34.—15 minutes.

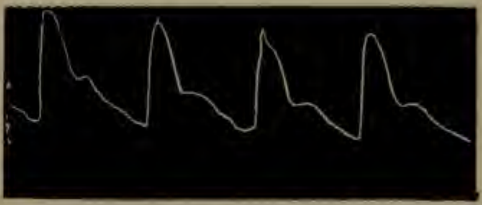


FIG. 35.—50 minutes.

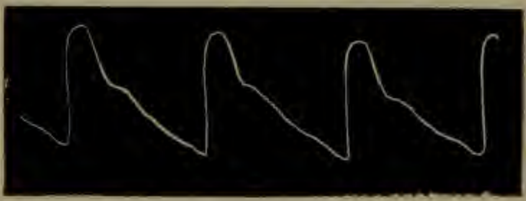


FIG. 36.—1 hour 50 minutes.

PLATE VI.

Nitro-Glycerine, ♏ i.

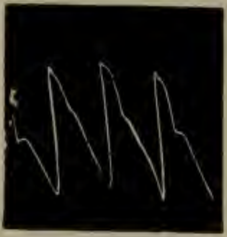


Fig. 37.—Normal.

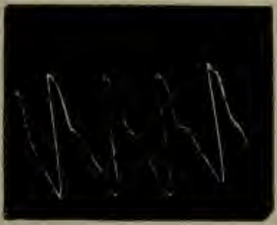


Fig. 38.—1 minute.

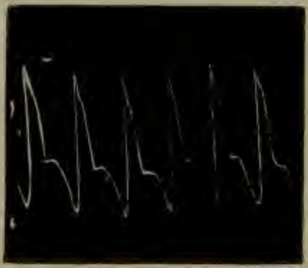


Fig. 39.—7 minutes.

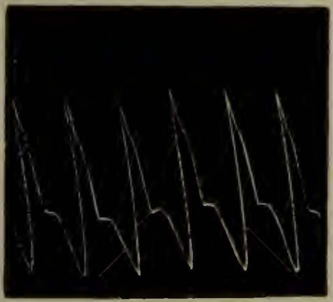


Fig. 40.—11 minutes.

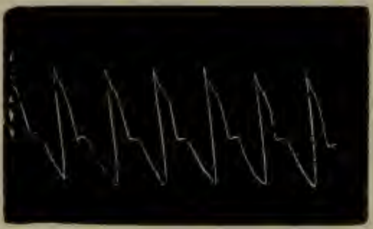


Fig. 41.—35 minutes.

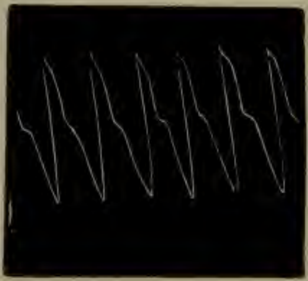


Fig 42.—75 minutes.

PLATE VII.

Nitro-Glycerine, ♏ iiss.

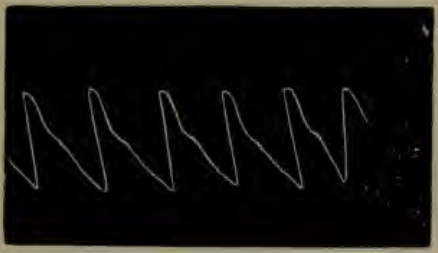


Fig. 43.—Normal.

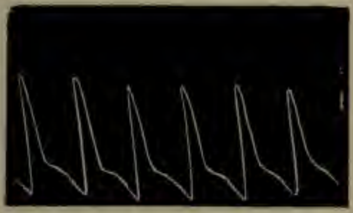


Fig. 44.—2½ minutes.

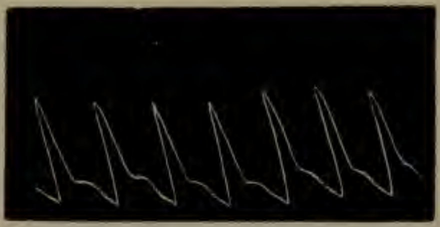


Fig. 45.—4 minutes.

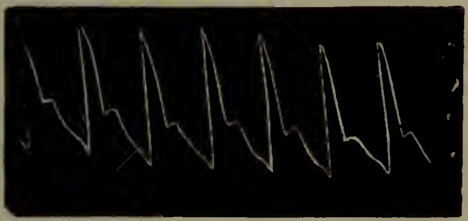


Fig. 46.—22 minutes.

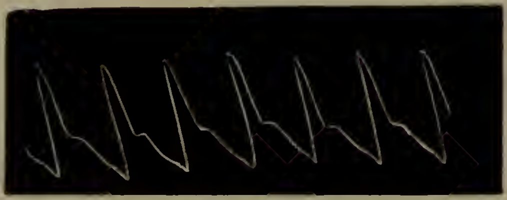


Fig. 47.—45 minutes.

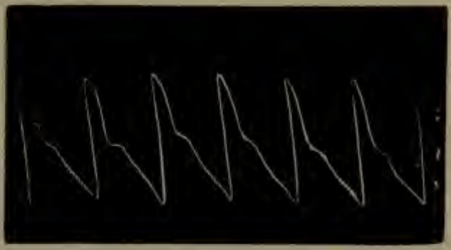


Fig. 48.—75 minutes.

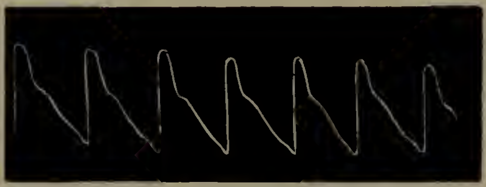


Fig. 49.—95 minutes.

PLATE VIII.

Nitro-Glycerine, ♏ iiiss.

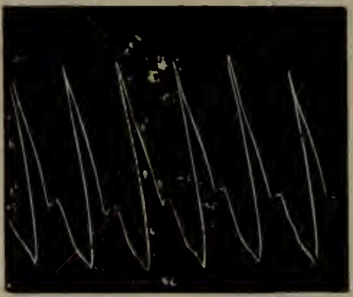


Fig. 50.—Normal.

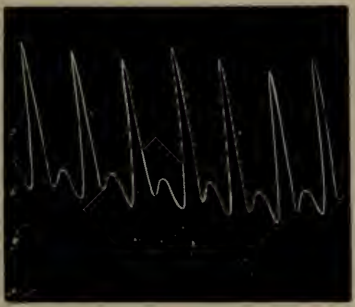


Fig. 51.—2 minutes 15 seconds.

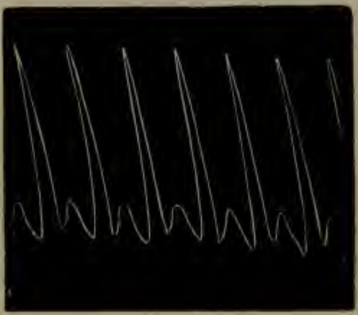


Fig. 52.—10 minutes.

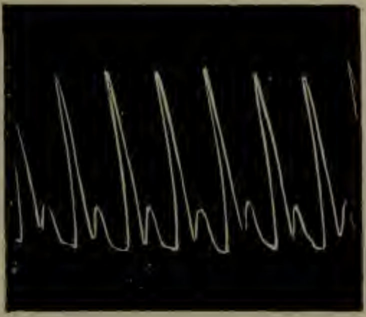


Fig. 53.—30 minutes.

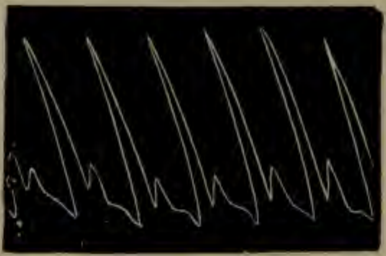


Fig. 54.—70 minutes.

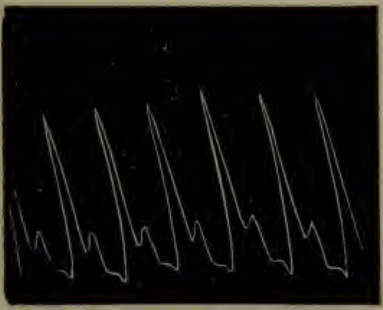


Fig. 55.—100 minutes.

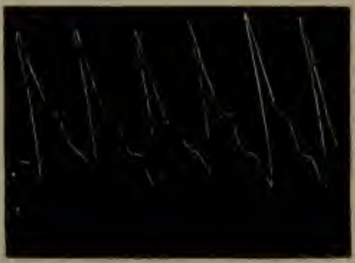


Fig. 56.—130 minutes.

PLATE IX.

Nitro-Glycerine, ♏

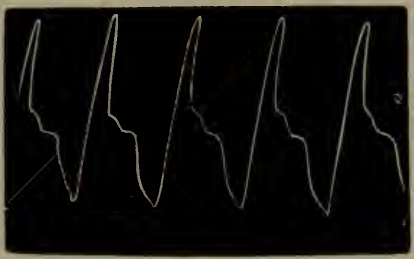


FIG. 57.—Normal.

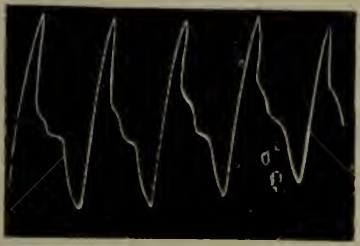


FIG. 58.—30 seconds.

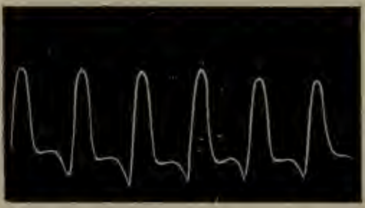


FIG. 59.—2 minutes.

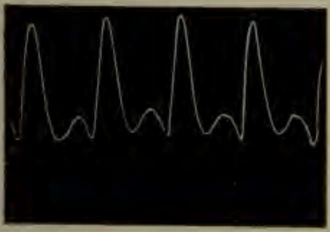


FIG. 60.—4 minutes 30 seconds.

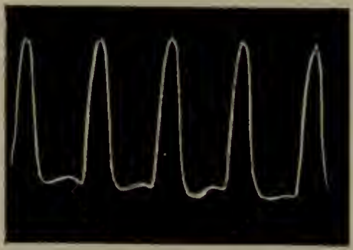


FIG. 61.—10 minutes.

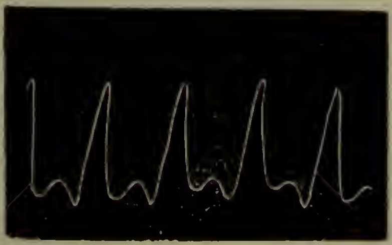


FIG. 62.—28 minutes.

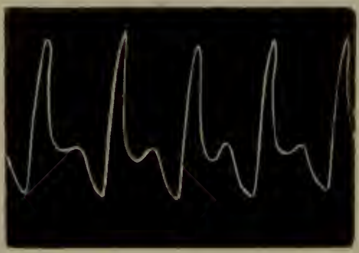


FIG. 63.—70 minutes.

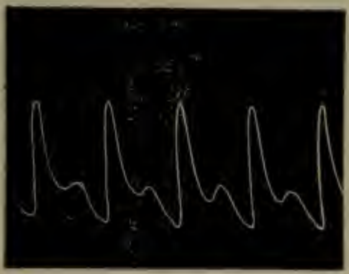


FIG. 64.—95 minutes.

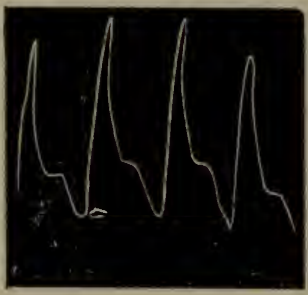


FIG. 65.—3 hours 25 minutes.

PLATE X.

Nitro-Glycerine, ♏ v.

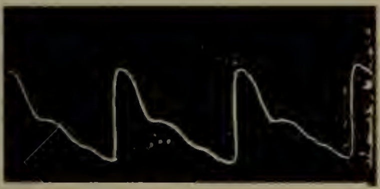


Fig. 66.—Normal.

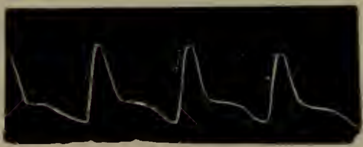


Fig. 67.—8 minutes.

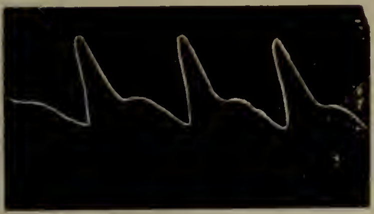


Fig. 68.—14 minutes.

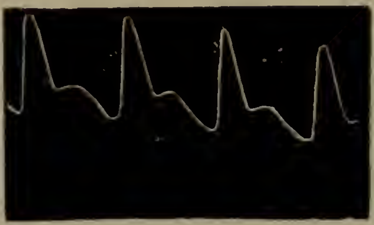


Fig. 69.—30 minutes.

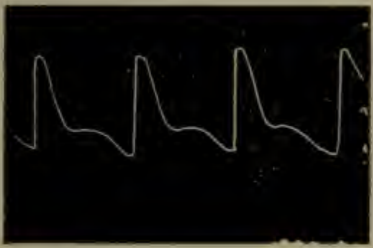


Fig. 70.—1 hour.

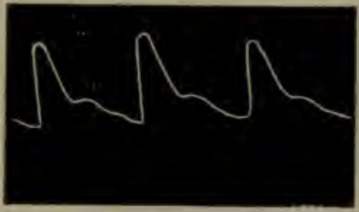


Fig. 71.—1 hour 40 minutes.

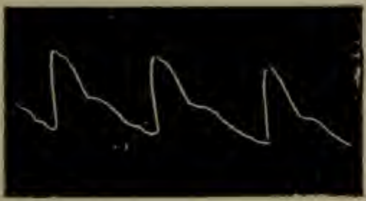


Fig. 72.—2 hours 40 minutes.

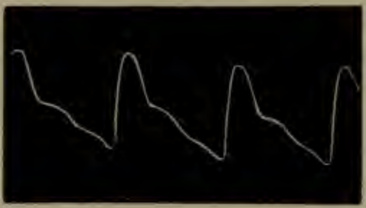


Fig. 73.—3 hours 30 minutes

PLATE XI.

Sodium Nitrite, grs. 5.

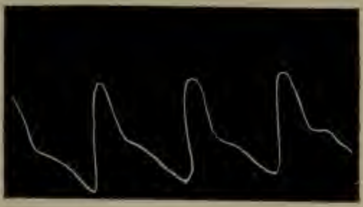


Fig. 74—Normal.

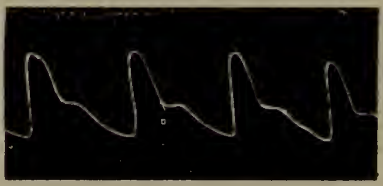


Fig. 75.—10 minutes.

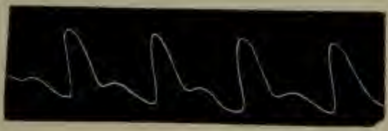


Fig. 76.—20 minutes.

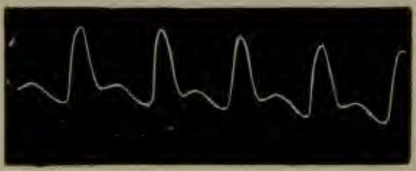


Fig. 77.—30 minutes.

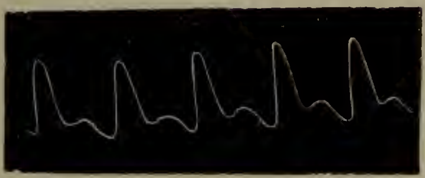


Fig. 78.—1 hour.

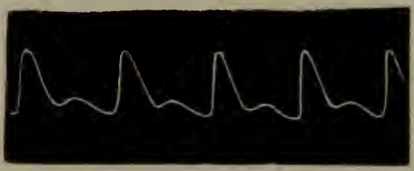


Fig. 79.—2 hours.

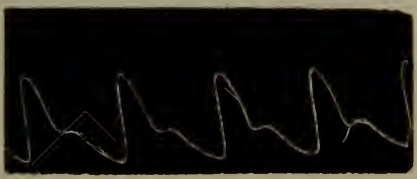


Fig. 80. –3 hours 30 minutes.

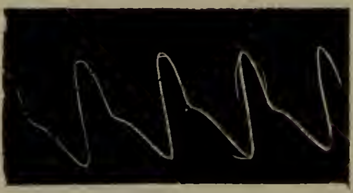


Fig. 81.—5 hours.

PLATE XII.

Potassium Nitrite, grains iv.

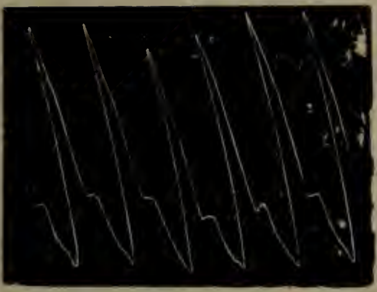


FIG. 82.—Normal.

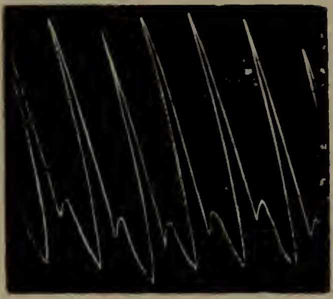


FIG. 83.—4 minutes 30 seconds.

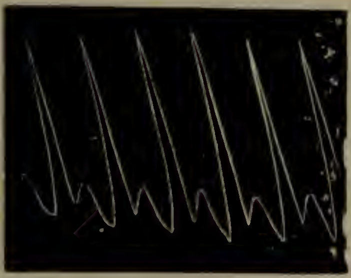


FIG. 84.—10 minutes.

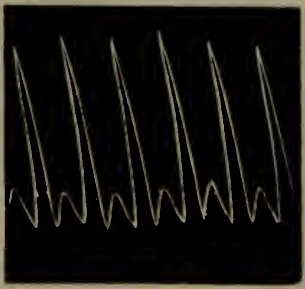


FIG. 85.—20 minutes.

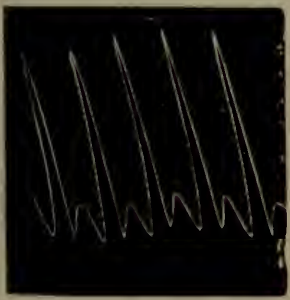


FIG. 86.—40 minutes.

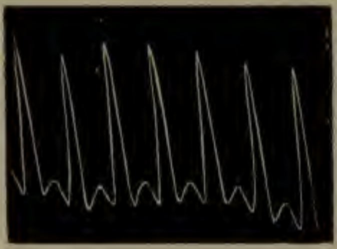


FIG. 87.—90 minutes.

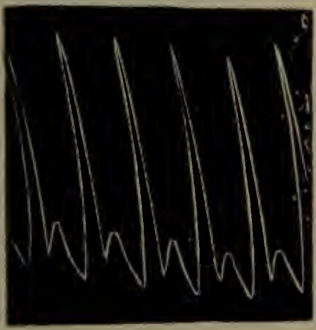


FIG. 88.—135 minutes.

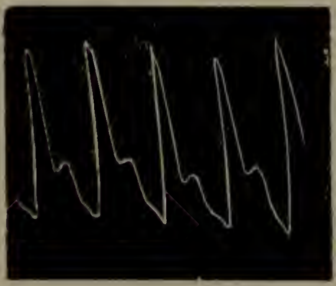


FIG. 89.—235 minutes.

PLATE XIII.

Sodium Nitrite, $\frac{1}{2}$ grain.

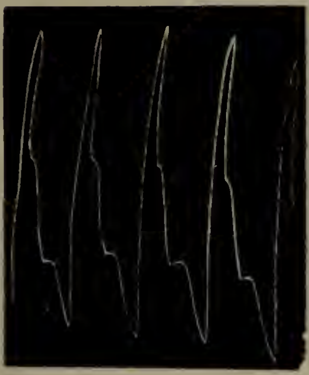


FIG. 90.—Normal.

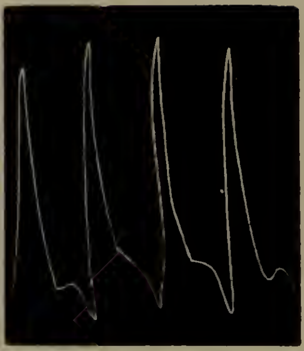


FIG. 91.—10 minutes.

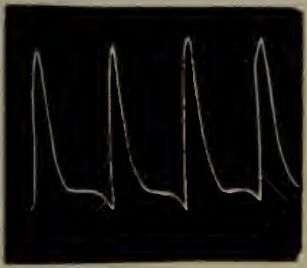


FIG. 92.—40 minutes.

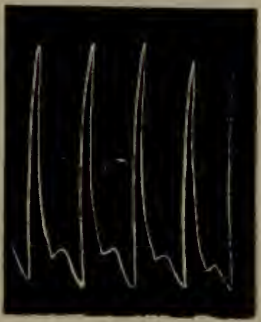


FIG. 93.—1 hour.

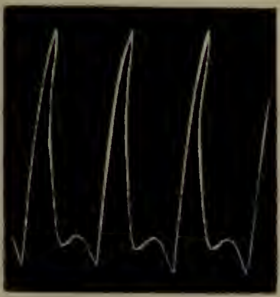


FIG. 94.—2 hours.

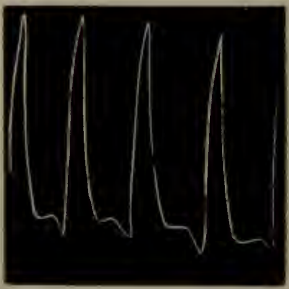


FIG. 95.—2 hours 50 minutes.

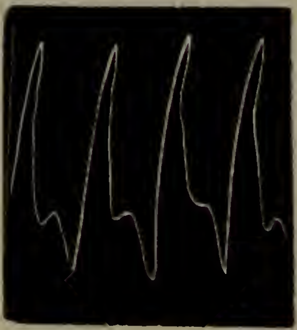


FIG. 96.—4 hours

PLATE XIV.

Cobalt Yellow, grains iv.

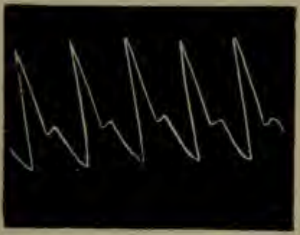


FIG 97.—Normal.

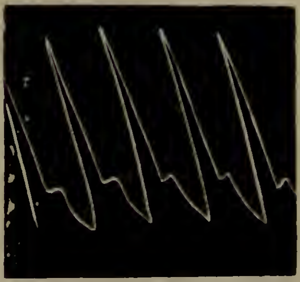


FIG. 98.—10 minutes.

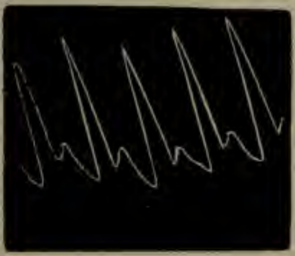


FIG. 99.—40 minutes.

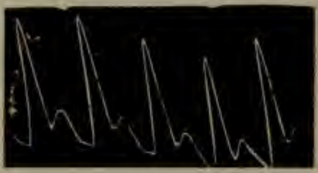


FIG. 100.—1 hour 40 minutes

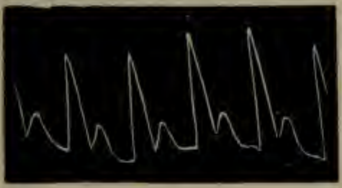


FIG. 101.—2 hours 40 minutes.

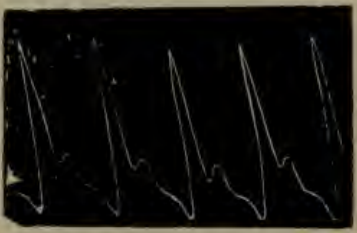


FIG. 102.—3 hours 40 minutes.

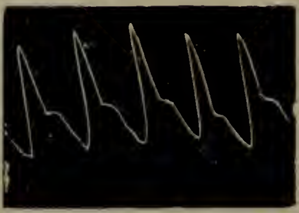


FIG. 103.—5 hours 10 minutes.

PLATE XV.

Cobalt Yellow, grains vii.

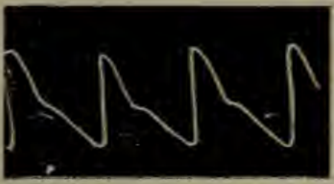


FIG. 104.—Normal.

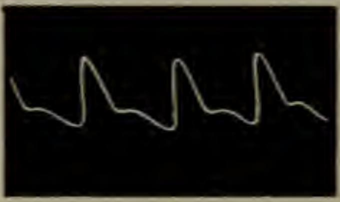


FIG. 105.—40 minutes.

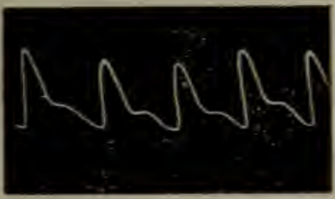


FIG. 106.—1 hour.

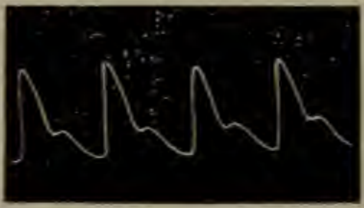


FIG. 107.—2 hours.

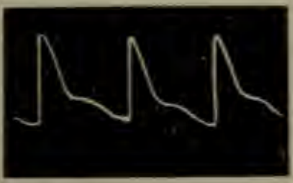


FIG. 108.—3 hours.

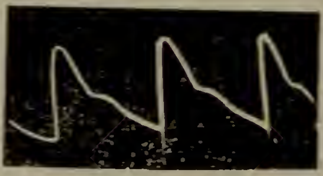


FIG. 109.—4 hours.

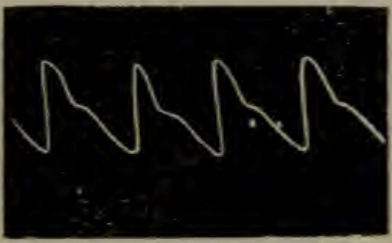


FIG. 110.—6 hours.

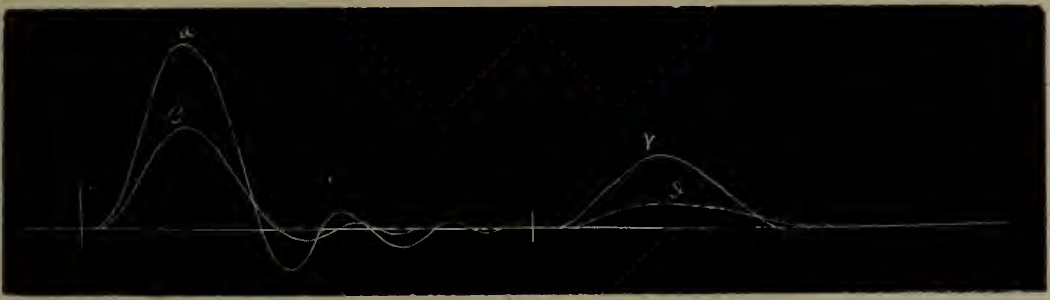


FIG. 111.—α Normal muscle curve immediately after preparation ; β after standing one hour in normal salt solution ; γ four hours after ; δ twenty-four hours after.

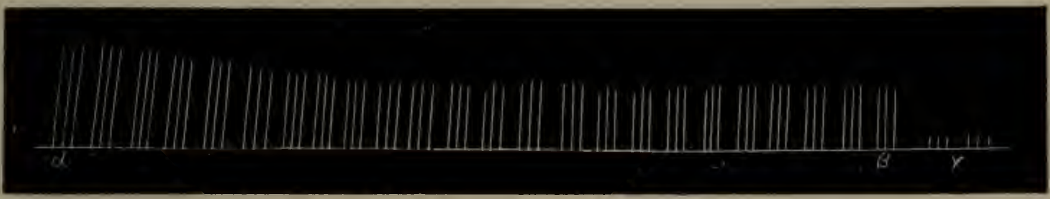


FIG. 112.—Muscle contractions recorded on stationary drum ; α to β at 5 minutes intervals for 6 hours ; γ after twenty-four hours.

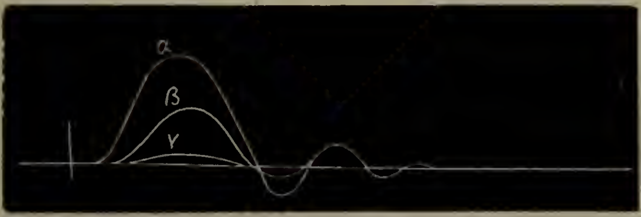


Fig. 113.—Muscle curve from gastrocnemius of frog showing the effect of 1 in 1,000 $NaNO_2$ in normal salt solution ; α, normal curve ; β, 14 minutes after addition of nitrite ; γ, 24 minutes after.

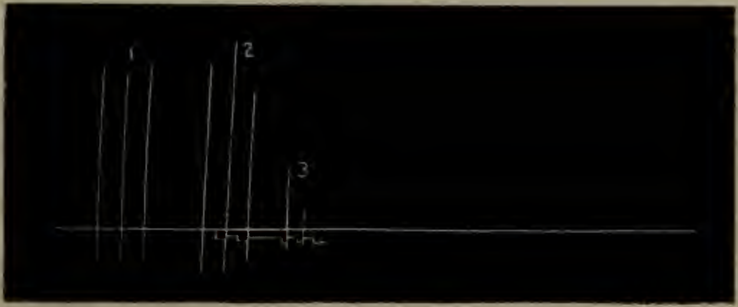


FIG. 114.—Tracing showing amplitude of contraction of muscle in 1 in 1,000 $NaNO_2$ solution ; (1) normal contractions ; (2) sodium nitrite introduced ; (3) contractions 15 minutes afterwards.

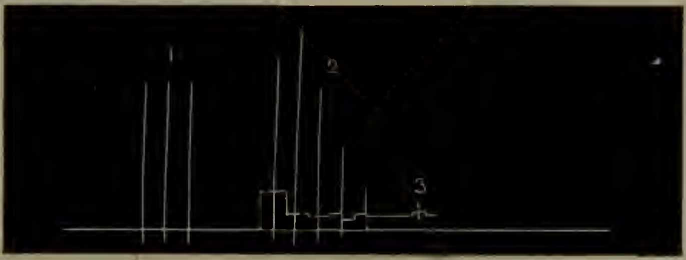


FIG. 115.—Tracing showing amplitude of muscle contraction in 0·75 per cent. $NaNO_2$ solution ; (1) normal contraction ; (2) 0·75 of sodium chloride solution replaced by 0·75 of sodium nitrite ; (3) 15 minutes afterwards.

PLATE XVII.

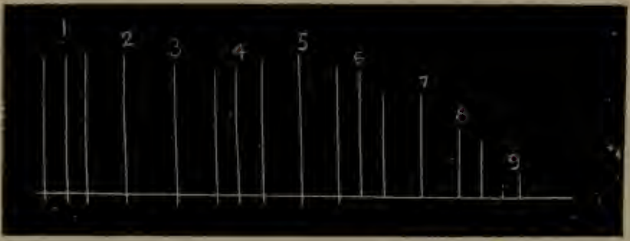


FIG. 116.—Tracing showing that nerve stimulation is as effective as direct stimulation of muscle when immersed in 1 in 1,000 $NaNO_2$ solution. (1) normal muscle contraction; (2) and (3) normal nerve contractions; (4) muscle; (5) nerve; (6) muscle; (7) nerve; (8) muscle; (9) nerve, after nitrite.

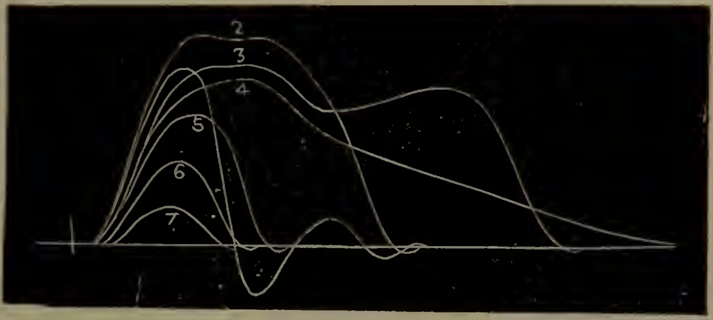


FIG. 117.—Barium chloride, 1 in 1,000; (1) curve with normal salt solution; (2) 15 minutes after barium chloride was added; (3) 20 minutes after; (4) 30 minutes after; (5) 45 minutes after; (6) 1 hour after; (7) 2 hours after.

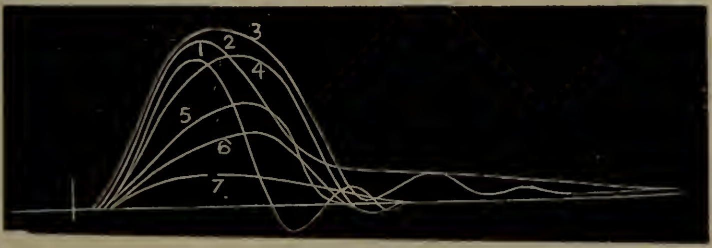


FIG. 118.—Barium nitrite, 1 in 1,000; (1) normal; (2) 6 minutes after barium chloride; (3) 12 minutes after; (4) 24 minutes; (5) 27 minutes; (6) 30 minutes; (7) 33 minutes.

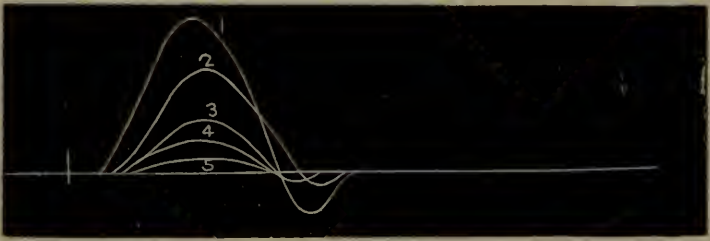


FIG. 119.—Barium nitrite, 1 in 5,000; (1) normal; (2) 10 minutes after barium chloride; (3) 15 minutes after; (4) 25 minutes; (5) 33 minutes.

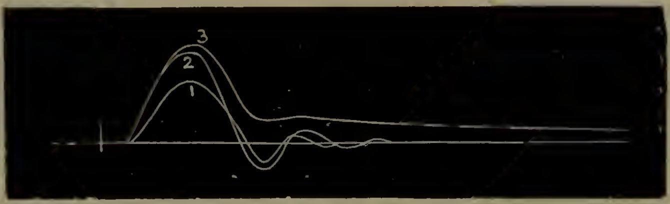


FIG. 120.—Calcium chloride, 1 in 1,000; (1) normal curve; (2) 1 hour after; (3) 5 hours after

PLATE XVIII.

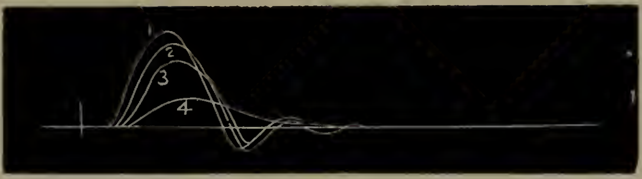


Fig. 121.—Calcium nitrite, 1 in 1,000; (1) normal tracing; (2) 1 hour after calcium nitrite; (3) 2 hours; (4) 3 hours.

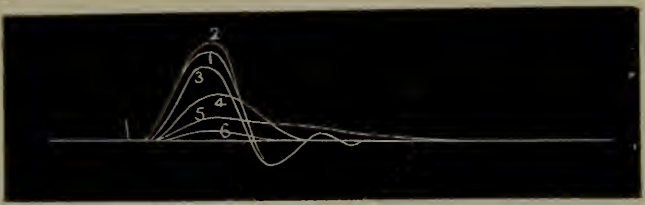


Fig. 122.—Calcium nitrite, 1 in 5,000; (3) normal; (2) one hour after calcium chloride; (1) 2 hours after; (4) 3 hours after; (5) 4 hours after (6) 5 hours.

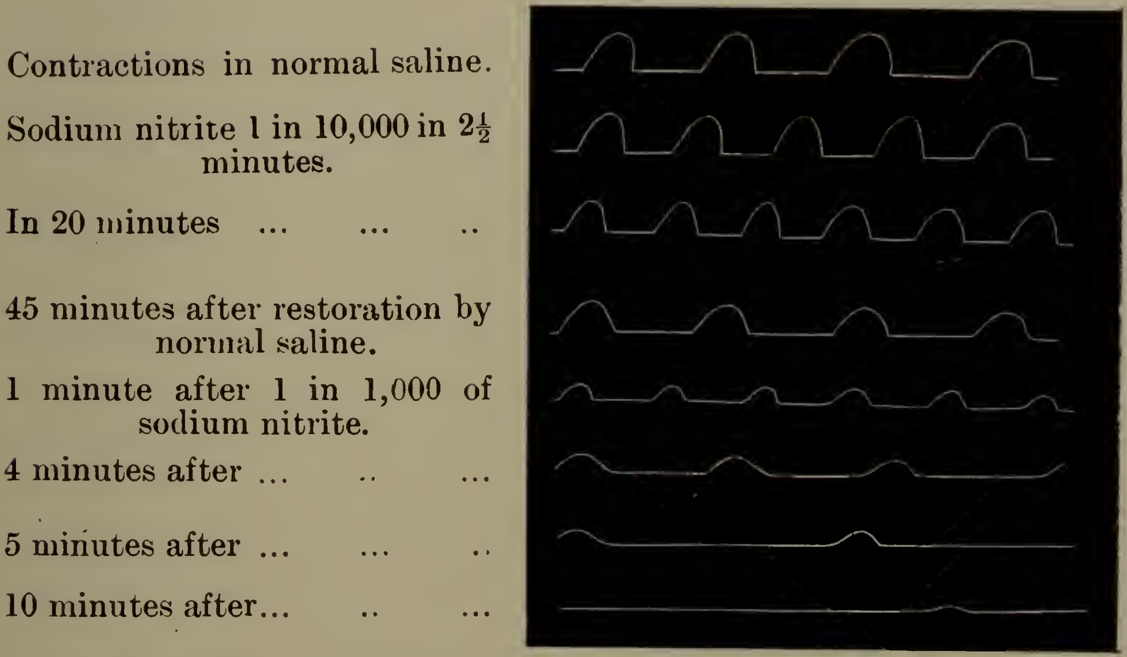


Fig. 123.—Effect of sodium nitrite on the separated frog's ventricle.

PLATE XIX.

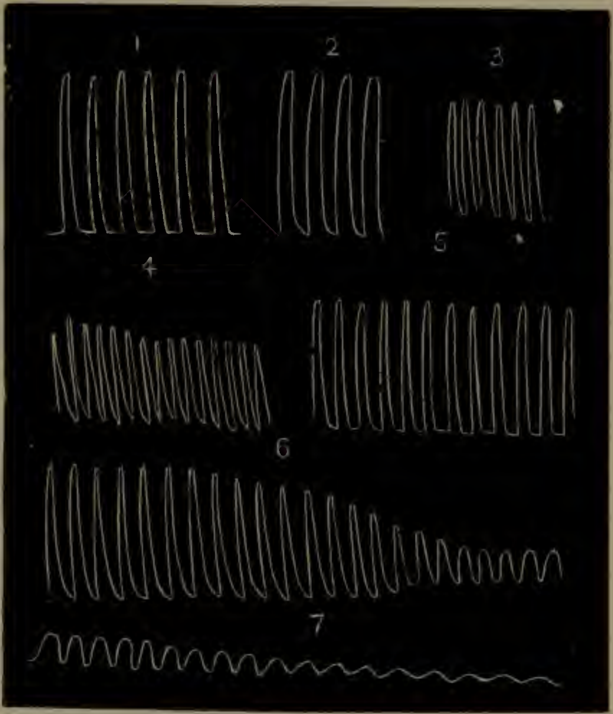


Fig. 124.—Effect of barium nitrite on frog's heart, 1 in 2,000 and 1 in 1,000. (1) Normal saline; (2) barium nitrite, 1 in 2,000; (3) 16 min. after; (4) 25 min. after; (5) barium nitrite replaced by normal saline 45 min.; (6) barium nitrite, 1 in 1,000; (7) 3 minutes after.

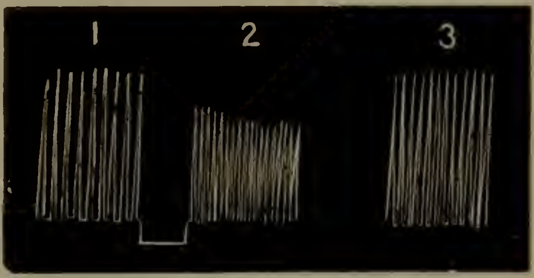


Fig. 125.—Influence of 1 in 4,000 of amyl nitrite in blood on the heart. (1) Beats with normal blood; (2) blood containing 1 in 4,000 of amyl nitrite used for 48 seconds; (3) normal blood used 3 min. Kronecker's apparatus.

PLATE XX.

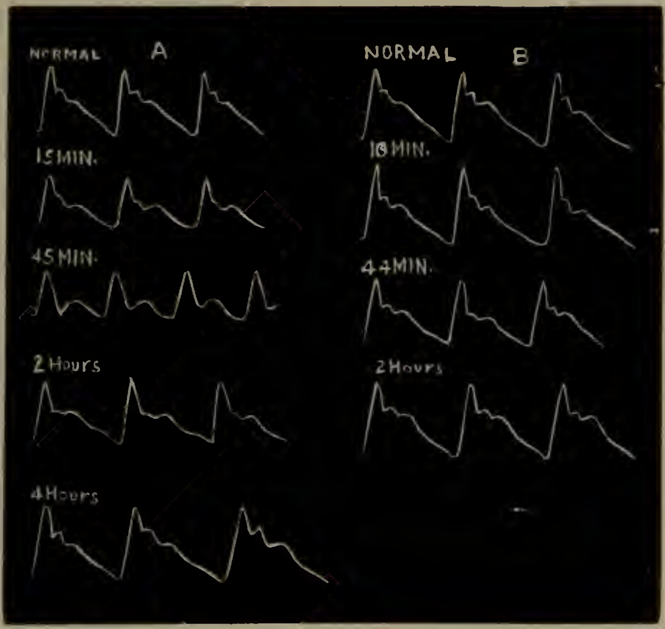


FIG. 126.
Sphygmogram, S.L.
Sodium nitrite, gr. ii.
A.—Oct. 5th, 1892. B.—Jan. 18th, 1893

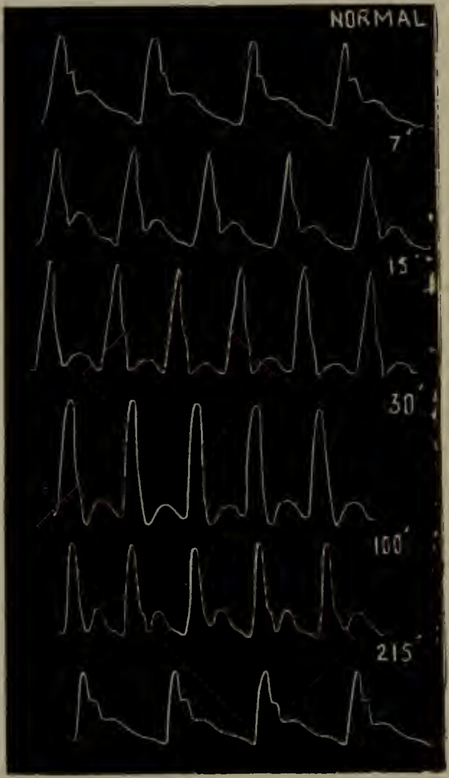


FIG. 127.
Sphygmogram, R.T.
Sodium nitrite, gr. ii.

PLATE XXI.

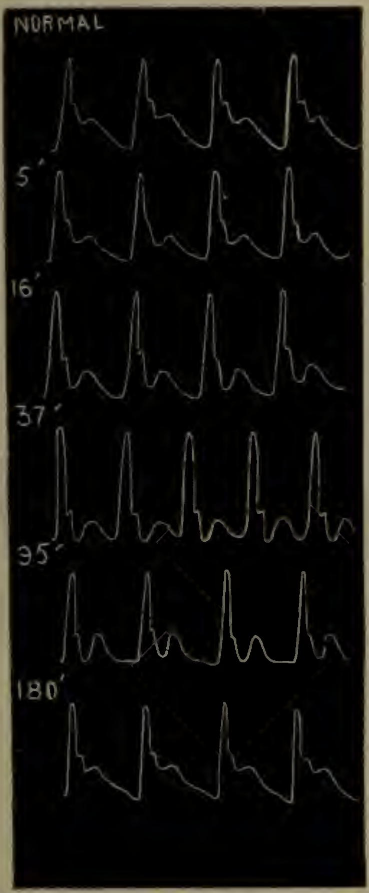


FIG. 128.

Sphygmogram.
Liq. ethyl nitritis,
dr. i

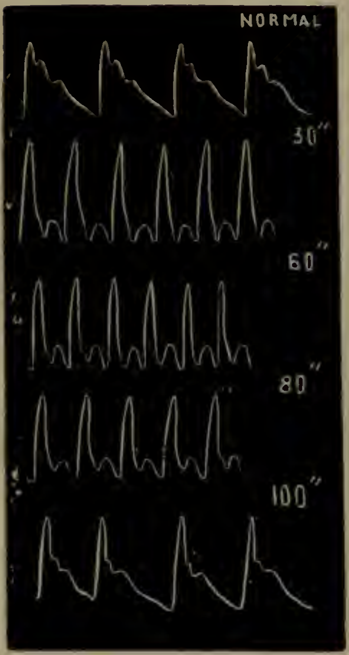


FIG. 129.

Sphygmogram.
Inhalation
propyl nitrite.

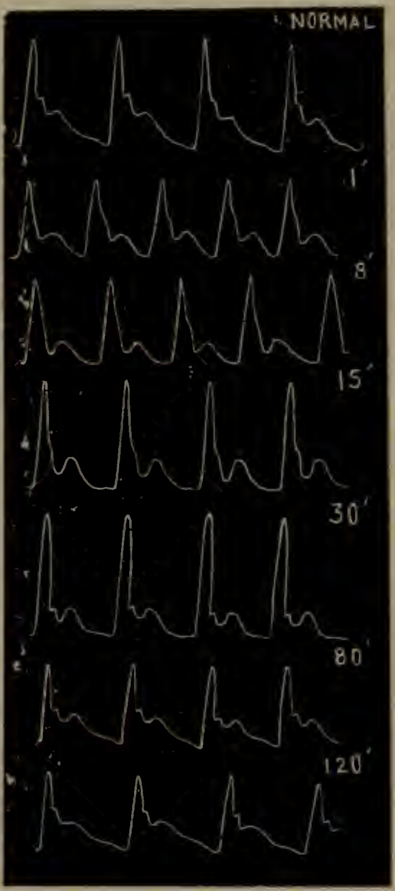


FIG. 130.

Sphygmogram.
Liq. trinitrinæ.
min. i.

PLATE XXII.

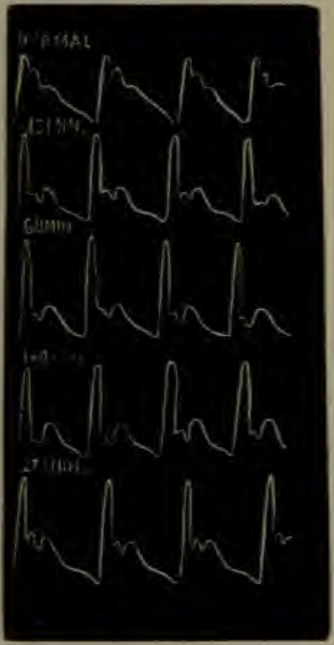


FIG. 131.

Sphygmogram.
Effect of amyl nitrite
when inhaled.

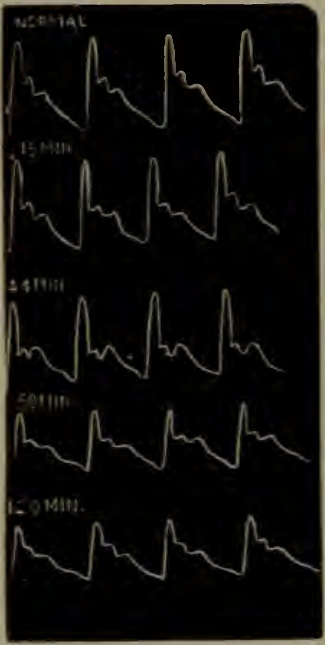


FIG. 132.

Sphygmogram.
Effect of amyl nitrite
when taken internally.

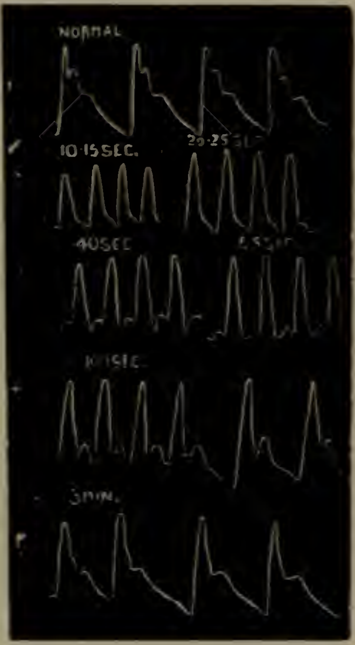


FIG. 133.

Sphygmogram.
Effect of amyl nitrate
when taken internally.

PLATE XXIII.

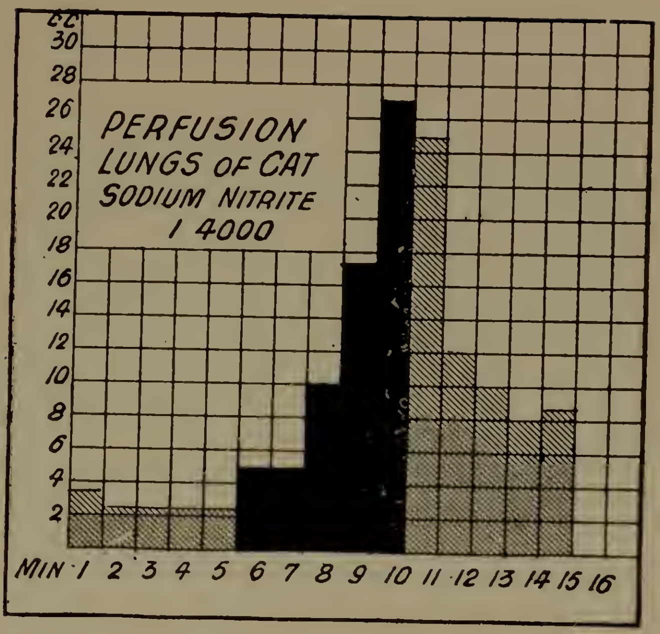


FIG. 134.—The figures at the base represent the number of minutes during which perfusion took place, those in the perpendicular line the number of c c.'s of blood passing through the lung. The lightly-shaded squares represent the flow whilst pure blood was passing through the vessels, the dark squares whilst nitrite blood was flowing.

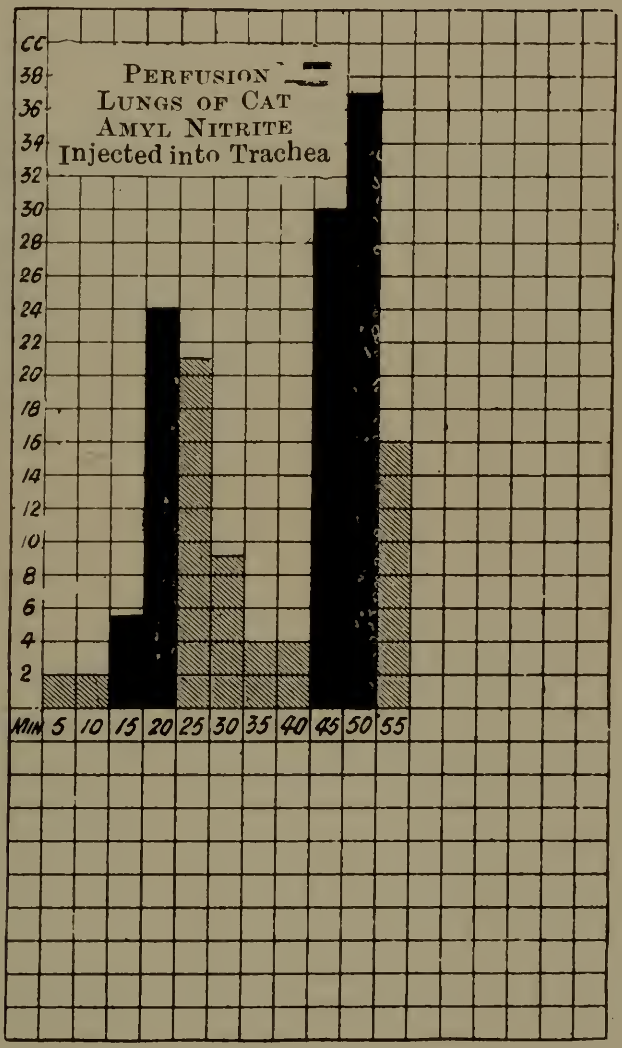


FIG. 135.

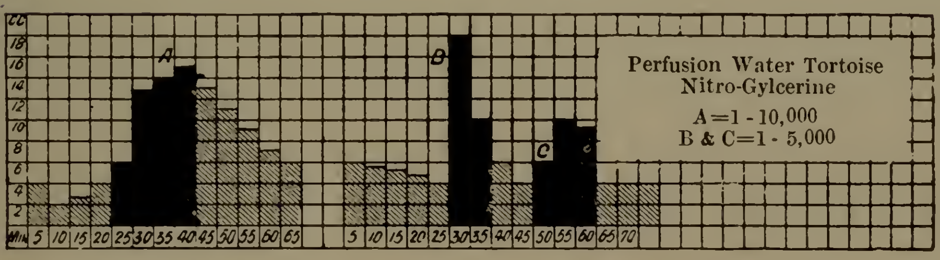


FIG. 136.

PLATE XXIV.

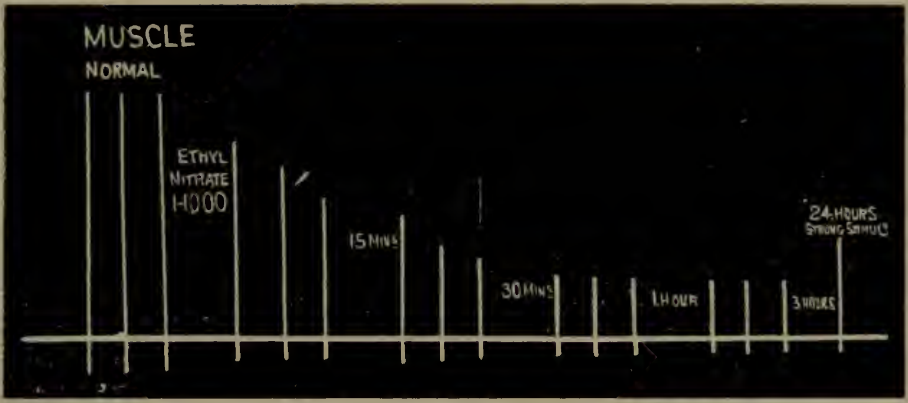


FIG. 137.—Muscle tracing on stationary drum. Ethyl nitrate 1-1000.

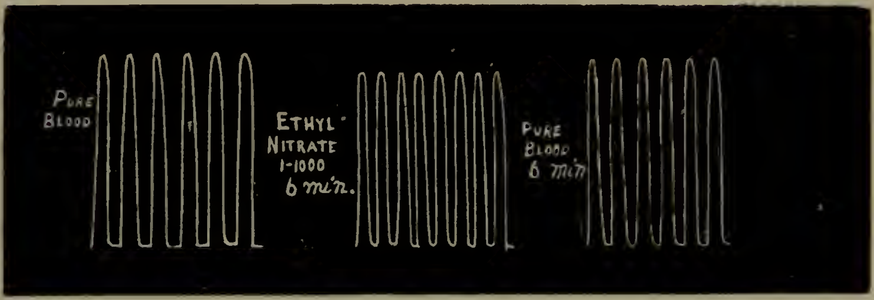


FIG. 138.—Heart tracing, Kronecker's apparatus. Ethyl nitrate, 1-1000.

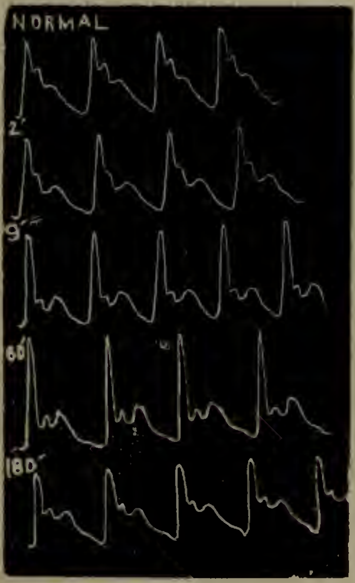


FIG. 139.
Sphygmogram S.L.
Ethyl nitrate, m. v.

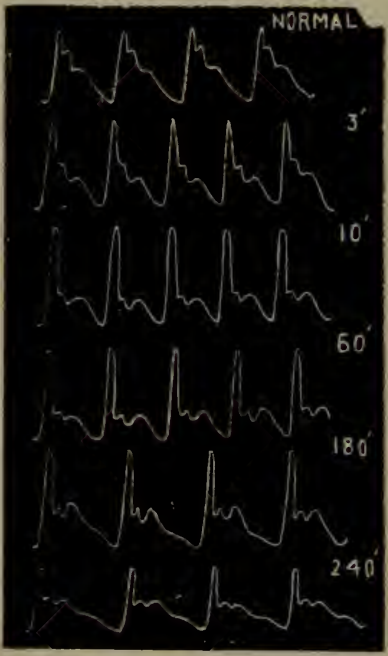


FIG. 140.
Sphygmogram S.L.
Propyl nitrate, m. v.

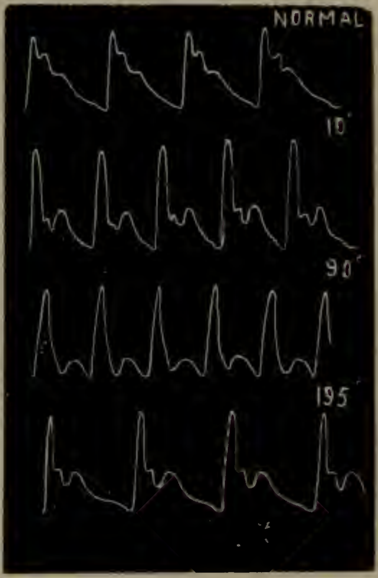


FIG. 141.
Sphygmogram S.L.
Isobutyl nitrate, m. x.

PLATE XXV.

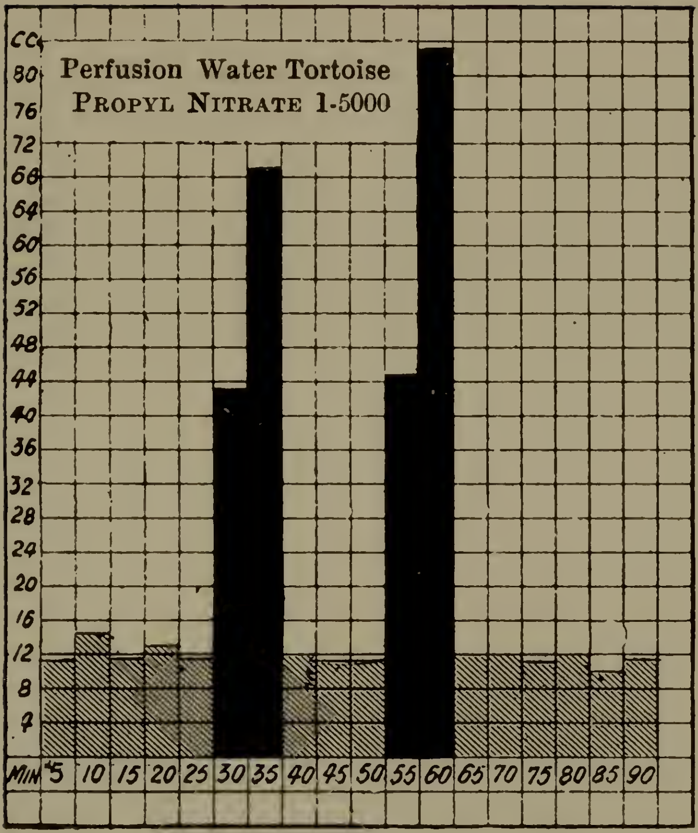


FIG. 142.—As in fig. 134, the figures at the base represent the number of minutes during which perfusion took place ; those in the perpendicular line the number of c.c. passing through. The light squares show the flow when normal salt solution passed through the vessels ; the dark squares when 1 in 5,000 of propyl nitrate was used.

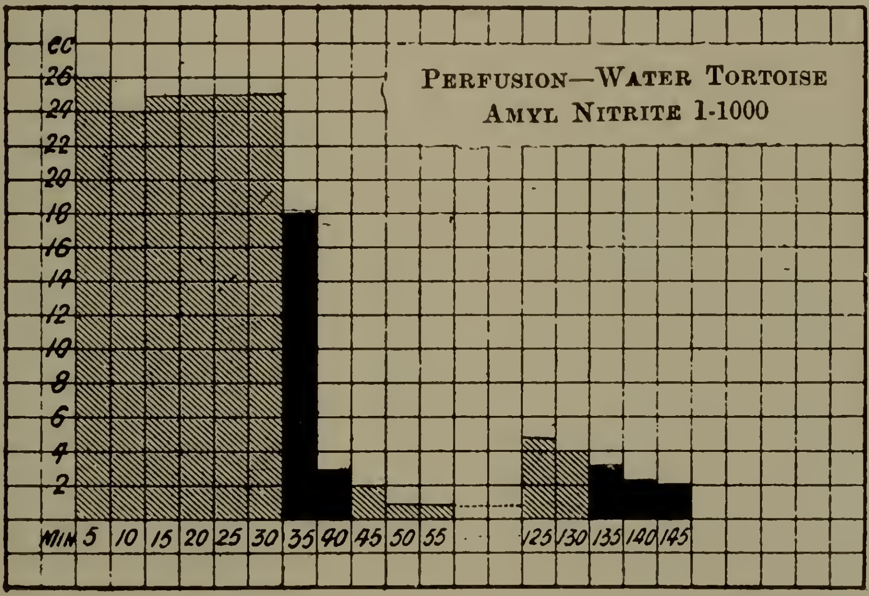


FIG. 143.

PLATE XXVI.

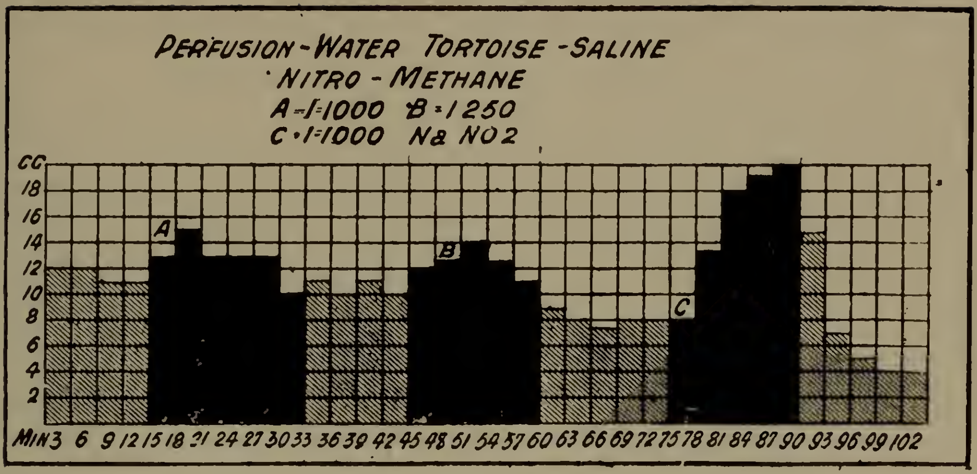
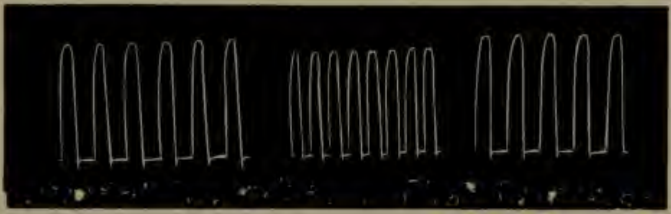


FIG. 144.—Nitro-methane followed by sodium nitrite.

6 min. after nitro-ethane, 1-1000.

Pure blood.



After pure blood 1 min.

FIG. 145.—Tracing taken from excised frog's heart with Kronecker's apparatus. Nitro-ethane 1-1000.

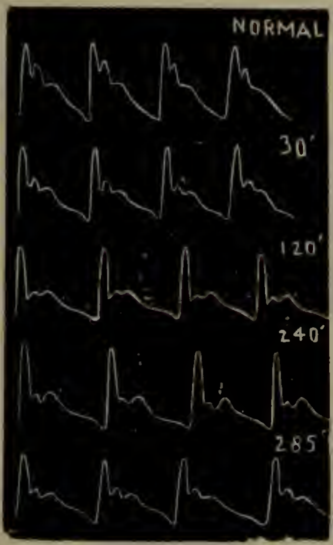


FIG. 146 —Sphygmogram, S.L. Nitro-ethane, m. xv.

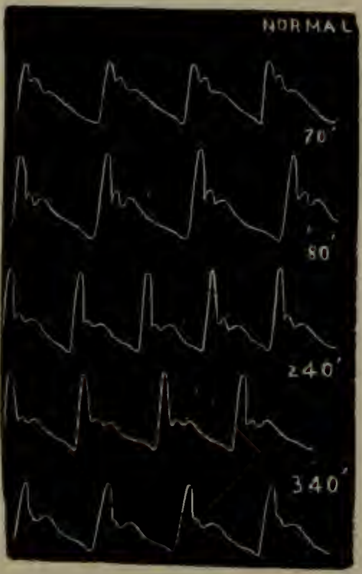


FIG. 150.—Sphygmogram, S.L. Nitro-pentane, m. x.

PLATE XXVII.

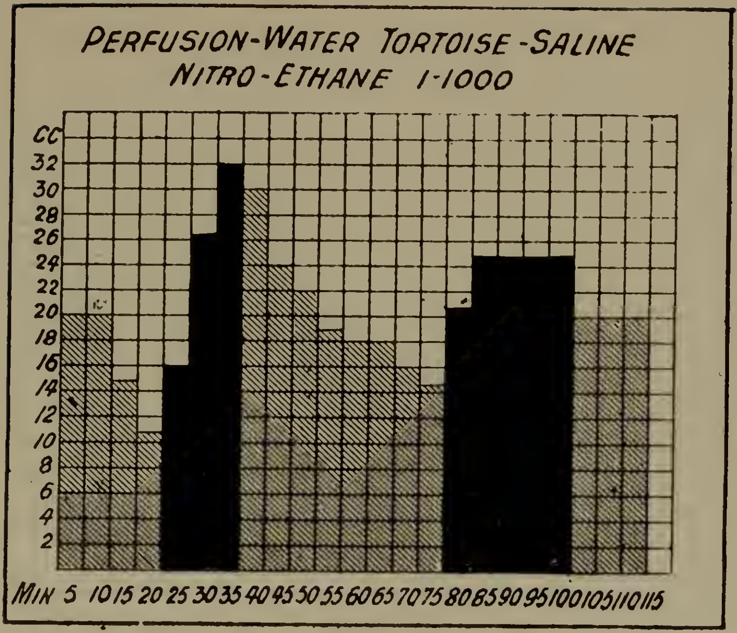


FIG. 147.

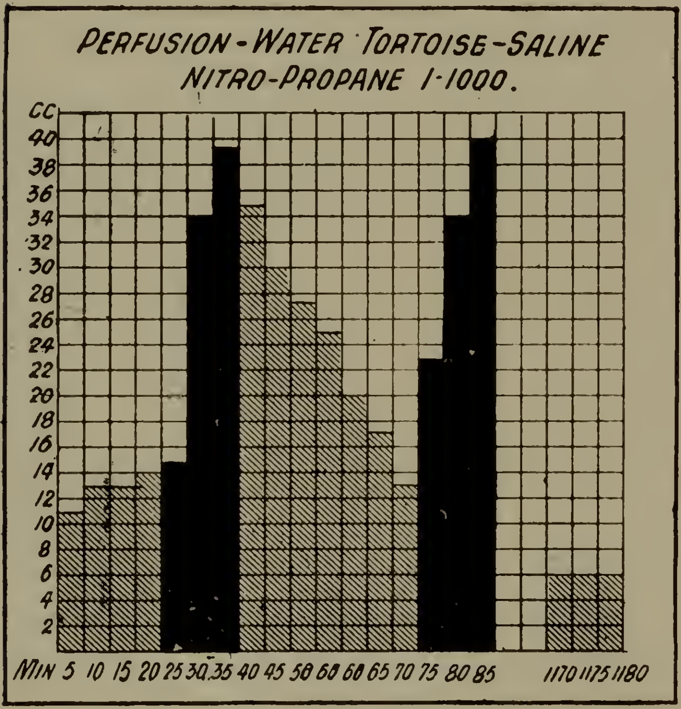


FIG. 148.

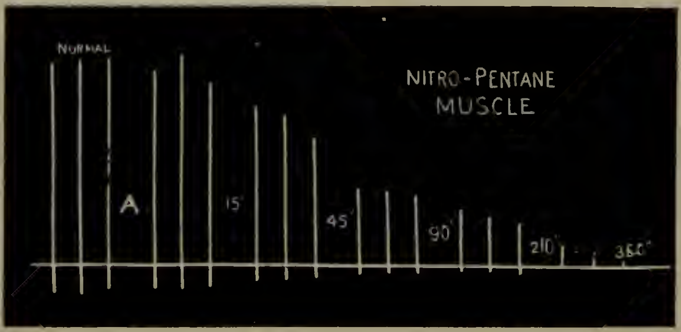


FIG. 149.—Muscle tracing on stationary drum. A. Nitro-pentane saturated solution in normal saline applied.

PLATE XXVIII.

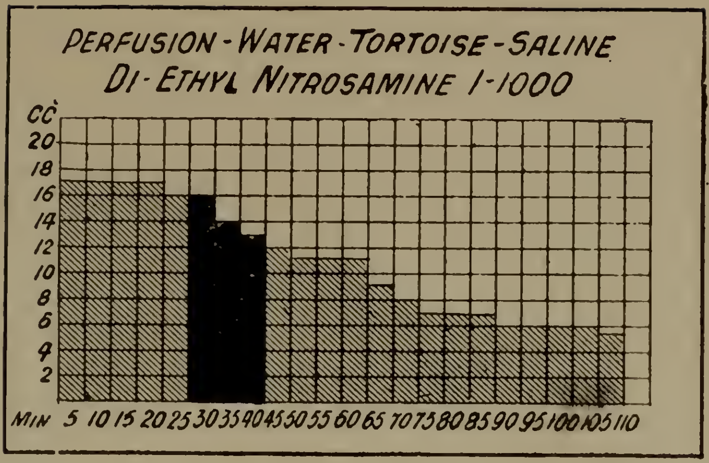


FIG. 151.

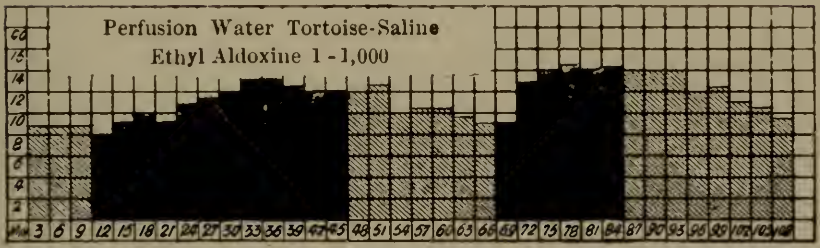


FIG. 152.—Ethyl aldoxine, 1-1000.

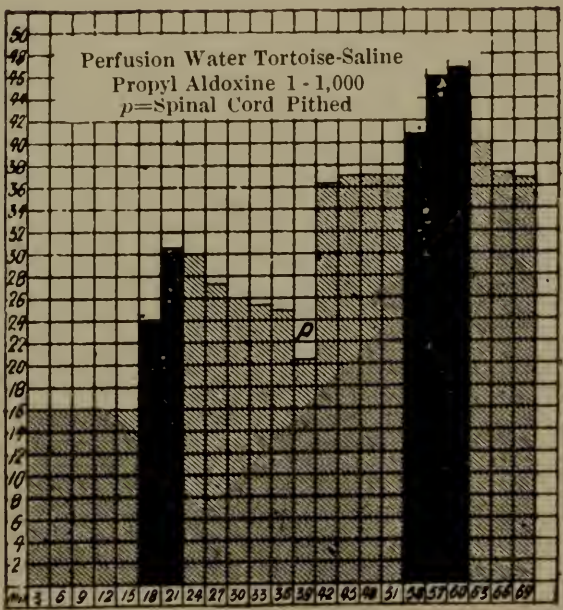


FIG. 153.—Propyl aldoxine, 1-1000.

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